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Pharmacology and Toxicology Review

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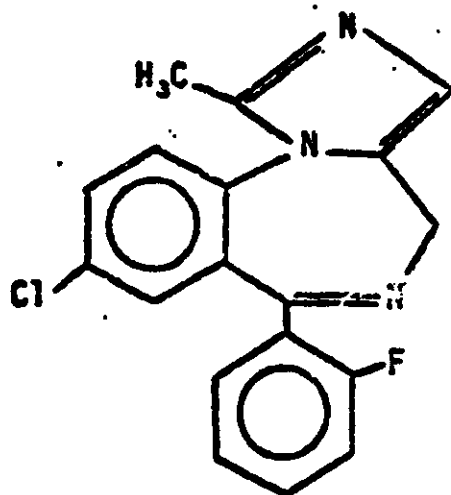
Sponsor: Hoffmann-La Roche, Inc.
Nutley, New Jersey 07110

Drug: Midazolam Injectable (RO 21-3981)

Category: Anesthetic premedicant as a sedative and inductive agent

Administration: Intramuscular or intravenous injection

Chemical Formula
and Name:



8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]-benzodiazepine

Chemical Forms Used in Preclinical Studies

RO 21-3981/000	Free base (Nutley formulation)
RO-21-3981/617	Free base (Basle formulation)
RO 21-3981/001	Maleate salt
RO 21-3981/002	Dihydrochloride salt
RO 21-3981/003	Monohydrochloride salt
RO 21-3981/602	Methanesulfonate salt

Related Drugs

The benzodiazepines. RO 21-3981 resembles triazolodiazepam derivatives; however, instead of a triazolo five member ring, it contains an imidazo five member ring. It also has a fluorine at the 2-phenyl position.

Related INDs:

Midazolam injectable:
Midazolam oral formulation:

Preclinical Pharmacological Studies with Midazolam

A. Neuropharmacology

Midazolam is an imidazobenzodiazepine whose salts are water soluble. When administered orally or parenterally to animals, it exhibits the characteristic pharmacological effects of marketed benzodiazepine drugs, i.e., anxiolytic (anti-conflict, calming effects), anticonvulsant, hypnotic, and muscle relaxant effects.

1. Continuous Avoidance Test in Rats

Midazolam maleate and diazepam have qualitatively and quantitatively similar effects in this test which measures a drug's ability to disinhibit behavior (avoidance) relative to conflict (electric shock). Typically, an anxiolytic drug at low dosage will increase the shock rate experienced by rats previously trained to avoid the shock rate experienced by rats previously trained to avoid the shock and then when the dose is raised to relatively high levels untoward effects such as sedation will result in greater escape failures. A wide separation of about 10 fold was observed for both drugs between the pharmacologically active dose and the neurotoxic dose.

2. Anticonvulsant, Pole Climbing and Rotorod Tests in Mice

Midazolam maleate (in water) and diazepam (in diazepam diluent) administered I.V. to mice were compared in the antimetrazol test for anticonvulsant activity and in the pole climbing and rotating rod tests for effects on muscle tone or coordination. Both drugs exhibited rapid onset of action in each test, with peak activity occurring at one minute after treatment. The potency of midazolam was 2-4 times that of diazepam at the peak time, but the duration of action for midazolam was shorter than that for diazepam. Specifically, in the antimetrazol test (which correlates well with clinical anxiolytic activity), diazepam was 2.5 times more potent than midazolam at one hour. In the pole climbing and rotarod tests diazepam was twice as potent as midazolam postdosing 30 and 15 minutes, respectively.

3. Muscle Relaxant Activity in Unanesthetized Cats

In unanesthetized cats the minimally effective dose of I.V. administered midazolam maleate was 0.25 mg/kg; diazepam was effective at 0.125 mg/kg. Both compounds showed a similar, rapid onset of activity (1-3 minutes). Duration of midazolam's activity was somewhat longer (46-90 minutes) than that of diazepam (20-35 minutes), a finding that was in contrast to results obtained in the mouse studies.

4. Hypnotic Activity in Mice

In mice diazepam and midazolam maleate I.V. displayed a rapid onset of hypnotic activity (0.3 minutes for diazepam and 1.1 minutes for midazolam, but the duration of action of midazolam (32 minutes) was only about half that of diazepam (57 minutes). The ED₅₀ (mg/kg I.V.) for diazepam was 18 mg/kg and for midazolam it was 70 mg/kg.

5. Neuromuscular and Spinal Cord Activity in Spinal or Decerebrate Cats

a) Neuromuscular Effects

In the unanesthetized spinal cat no effect on the amplitude of contraction of the muscle was produced by either midazolam maleate (0.01-30 mg/kg, I.V.) or diazepam (0.01-20 mg/kg, I.V.).

b) Dorsal Root Potential (DRP)

In the unanesthetized spinal or decerebrate cat, diazepam produced an increase in the amplitude and duration of the DRP, an effect that is interpreted as one indicator of an enhancement of presynaptic inhibition. The minimal effective dose was 0.05, I.V. and all doses up to 3 mg/kg were active. Midazolam maleate was qualitatively similar to diazepam but was less potent, with a minimal effective dose of 0.1 mg/kg, I.V. Both agents had an onset of action that occurred within 1 minute after injection; however, they differed markedly with respect to duration. After injection of midazolam, the DRP returned to control value within 30 minutes, whereas after injection of diazepam, the DRP continued to be enhanced for at least 4 hours.

c) Effect on the Gamma-Aminobutyric Acid (GABA) System

Current hypotheses propose that diazepam enhances presynaptic inhibition by means of an action on GABA neurons. In experiments related to this proposal, midazolam maleate was found to be qualitatively similar to diazepam. At the DRP peak-effect dose level of 1 mg/kg, I.V. in cats either agent reversed the depression of the DRP produced by the GABA blocking agent, bicuculline (0.3-0.6 mg/kg, I.V.). In addition, the enhancing action of either compound on the DRP was blocked by a GABA depletor, semicarbazide (200 mg/kg, I.V.) given 4 hours before the test drug.

B. Cardiovascular and Respiratory Studies in Dogs**1. Conscious Dogs**

Midazolam was administered by I.V. injection to female renal hypertensive dogs at doses of 0.3, 1, 3, and 10 mg/kg. All dogs appeared to be excited immediately after injection. The blood pressure was not altered. Heart rate, however, increased up to 20-25% after all dosages at varying times after injection. The heart rate was essentially normal 120 minutes post dosing.

2. Anesthetized Dogs

Midazolam maleate (4-20 mg/kg, i.v.) induced transient blood pressure (systolic and diastolic) reductions of 25-40 mm Hg in dogs anesthetized with barbiturate and 20-55 mm Hg in chloralosed dogs.

Decreases of approximately 30% in minute volume of respired air occurred in both groups of animals. Myocardial impairment was not reflected in the right atrial pressure of any of the treated animals. No significant effects on ECG were observed after midazolam administration.

Midazolam did not alter the pressor responses to injected epinephrine, norepinephrine, hypertensin or dimethylphenyl piperazinium (DMPP). Pressor responses to serotonin and to carotid artery occlusion were somewhat inhibited. Depressor responses to acetylcholine or histamine administration were essentially unaffected by midazolam.

C. Drug Interactions in Animals

Effects of midazolam alone or in combination with other drugs commonly used in preanesthetic medication.

1. Cardiovascular and Respiratory Studies

Animals:

Dogs: 4 females, weight 8.1-9.2 kg. The dogs were trained to be conscious when the experiments were carried out.

Dosage, route and duration of each drug:

- 1) Midazolam maleate - I.V. (0.15 mg/kg)
- 2) Hydroxyzine HCl (Vistaril, Pfizer) - I.M. (0.7 mg/kg)
- 3) Atropine sulfate (Burroughs Wellcome) - I.M. (0.007 mg/kg)
- 4) Meperidine HCl (Wyeth) - I.M. (1 mg/kg)

Sequence of Administration:

	<u>No. of animals*</u>	<u>Time in Minutes</u>		
		<u>0</u>	<u>60</u>	<u>120</u>
Protocol A	3	(2) (3) + (4)	saline	
Protocol B	4	(2) (3) + (4)	midazolam	
Protocol C	4	saline	saline	midazolam

*The animals were randomized and there were two days of rest between treatments.

Observed effects:

Systolic, diastolic and mean blood pressure were slightly decreased in protocol A 10 minutes after administration of drugs; whereas they were all elevated by 20-30 mm Hg in protocol B and C 10 minutes after dosing. The consistent, slight increase in blood pressure was transient. Fifteen minutes after midazolam treatment all returned to normal levels. Venous pressure decreased 15 minutes after midazolam in protocol B. Heart rate and pulse pressure remained relatively unchanged in all protocols. Respiratory rate was slightly elevated in protocol B and C 10 minutes after midazolam but by 30 minutes it returned to normal. Cardiac index (slightly decreased at 60 minutes in protocol B and C), stroke index (slightly decreased at 60 minutes in protocol B) and peripheral resistance index (slightly increased at 60 minutes in protocol A, B, and C) were found to be relatively competent. No observable changes were noted in the ECG wave form or blood gas data in the 3 protocols.

Conclusion:

The combination of midazolam and commonly used preanesthetic medications (atropine, meperidine, hydroxyzine) seems to exert only minor effects on cardiovascular and respiratory systems. There were transient increase in blood pressure and respiratory rate, but they returned to normal within a short period of time.

2. Dose Lethality Response of Midazolam, its Vehicle and Various Preanesthetics:**Animals:**

CD-1 mice from Charles River, Inc. weight 17-25 gm. 10 sex/dose level

Dosage:**Preanesthetics given orally:**

- 1) Meperidine HCl: 200-630 mg/kg for males and females.
- 2) Atropine sulfate: 500-1000 mg/kg for males; 400-1250 mg/kg for female.

- 3) Meprobamate: 1000-2000 mg/kg for males and females.
- 4) Sodium Pentobarbital: 125-320 mg/kg for males and females.
- 5) Chlorpromazine HCl: 630-1250 mg/kg for males and females.

Midazolam maleate (3 mg/kg) or vehicle (0.024 ml/20 gm body weight) were administered I.V. 5 minutes following meperidine HCl, sodium pentobarbital or atropine sulfate, 30 minutes after chlorpromazine HCl and 60 minutes after meprobamate. All groups of animals were observed for 72 hours.

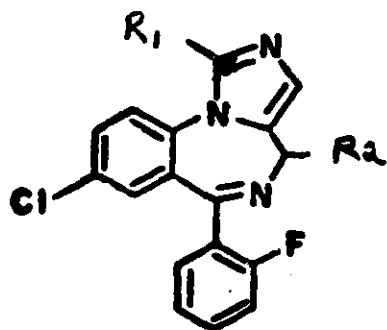
Conclusion:

An increase in lethality was consistently observed after combination of midazolam and chlorpromazine. Such an increase in lethality may also have occurred when midazolam was combined with atropine and pentobarbital. The cause of death was probably due to respiratory depression caused by high doses of the drugs.

Pharmacokinetics and Metabolism Studies with Midazolam

Studies have been conducted in vitro and in mouse, rat, and dog following intravenous administration of ^{14}C midazolam.

In Vitro



	R ₁	R ₂
I.	CH ₃	H (midazolam)
II.	CH ₂ OH	H (Ro 21-6347)
III.	CH ₃	OH (Ro 21-5975)
IV.	CH ₂ OH	OH (Ro 22-0284)

Midazolam metabolites formed after in vitro incubation with rat liver 9000 X g supernatant.

In Vivo

1. Mouse (male, CD-1)

Labelled drug (4.6 mg/kg) was given intravenously in order to determine the tissue distribution of drug and metabolites during the first 60 minutes after its administration. Correlations were also sought between CNS activity and brain levels of drug and metabolites.

Midazolam accounted for 85% of the radioactivity in the brain at 1 minute. Within 10 minutes after I.V. dosing less than 50% of the radioactivity in plasma, brain, muscle, lung and fat was present as unchanged drug. At no time did the radioactivity in tissues exceed that in plasma. The half-life of intact drug in the brain was about 5 minutes. Moreover, the rate of disappearance of midazolam from the brain in the first 30 minutes was more rapid than its disappearance from the other tissues. Two metabolites RO 21-6347 and RO 21-5975 were also identified. The tissue levels, excluding brain, of RO 21-6347 were 5-10 fold higher than RO 21-5975. In general, very low concentrations of RO 21-5975 were found in brain with peak levels observed at 20 minutes post dosing. RO 21-6347 was present in brain at higher concentrations than midazolam or RO 21-5975 at 20 minutes.

With respect to the pharmacological CNS activity of midazolam and its two metabolites, it was found that the inhibition of anticonvulsant activity (metrazol and bicuculline) and ataxia were due to midazolam and not to RO 21-6347 or RO 21-5975.

2. Rat (male, CRCD)

Ether anesthetized rats were administered [¹⁴C]-midazolam (2.5 mg/kg) into the tail vein. Tissue samples were collected at 30 minutes, 1, 3, 5, 7 and 24 hours after dosing. Urine and feces were also collected.

Within 30 minutes about 50% of the radioactivity was found in the GI tract. At 24 hours, 8% was present in the GI tract while 80 and 9% were excreted in the feces and urine, respectively. Only about 2% of the administered dose remained in other tissues after 24 hours. Less than 1% of the dose was identified as midazolam, or unconjugated RO 21-6347 and RO 21-5975. The tissue distribution of radioactivity was highest in liver followed by kidney and fat. In another experiment using bile-duct cannulated rats, 50% of an I.V. dose of [¹⁴C]-midazolam was excreted in the bile during a 3 hour period following dosing. Phenolic metabolites were isolated from the bile and included RO 22-0284 and RO 21-5975. The biliary metabolites were excreted as glucuronide or sulfate conjugates.

3. Rat placental transfer of [¹⁴C] - midazolam

Fetal levels of radioactivity were less than levels in maternal blood or in the placenta suggesting a slower or limited penetration through the placenta.

4. Dog (male, Beagle)

Dogs were administered a single I.V. injection (10 mg/kg) of [¹⁴C] midazolam

Tri-exponential blood level time curves were obtained in dogs. A three compartment open system was described - one central and two peripheral. The

apparent half-life of elimination of midazolam was calculated to be 67 minutes. Fifty percent of the administered radioactivity was excreted in the feces. The total recovery of administered radioactivity ranged between 77-88% for 72 hours. RO 21-6347 was the major metabolite and accounted for 29-40% of the administered dose. Small amounts of midazolam and a trace of RO 21-5975 and RO 22-0284 were also present. In urine RO 21-6347 was excreted primarily as its glucuronide conjugate. It was not conjugated in the feces, but probably eliminated by the bile as its glucuronide and hydrolyzed by bacteria in the large intestine.

5. Human (men, 70-80 kg)

Five men were administered midazolam by I.V. injection of 0.13 mg/kg in 1 minute.

In 4 men, the blood fall off curves were triexponential and would be fitted to a three compartment system with elimination occurring from the central compartment. Midazolam is rapidly and extensively distributed and eliminated from the body with a half-life of 1.3 to 2.2 hours.

Three urinary metabolites were identified as glucuronides: RO 21-6347, RO 21-5975 and RO 22-0284. The major metabolite RO 21-6347, which accounted for 50% of the administered dose, was eliminated primarily within the first 12 hours. The overall recovery of the administered dose as this metabolite was 45-57% within 72 hours.

Conclusion:

Animal and clinical pharmacokinetic studies after I.V. injection of midazolam demonstrated that it and its metabolites appeared to be distributed rapidly and eliminated rapidly. Midazolam undergoes biotransformation by hydroxylation and conjugation before elimination from the body. The half-life in dogs was about 1 hour and in man it was about 1-2 hours. In dogs the urinary recovery of RO 21-6347 glucuronide was about 40% of the administered dose by 72 hours. In man, the urinary recovery of this metabolite was about 50% by 72 hours. Thus, the pharmacokinetic and metabolic profile of midazolam after I.V. injection appears similar for dog and man.

Preclinical Toxicology

1. Acute Parenteral Toxicity

Mice	I.V., I.M.
Rats	I.V., I.h.
Rabbits	I.V., I.M.
Dogs	I.V.

2. Single-Dose Studies

Rabbits I.V. (venous irritation, 3 studies)
I.M. (muscle irritation, 2 studies)

Dogs I.V. (venous irritation, 2 studies)

3. Pyramiding - Dose Toxicity

Dogs I.M.

4. Subchronic Toxicity

Rats I.M. (2 weeks)
I.V. (5 weeks)

Rabbits I.V. (2 weeks)
I.V. (2 week treatment; 2 week and 12 week observation)
I.V. (2 week treatment; 19 week observation)

Dog I.M. (2 weeks)
I.V. (2 weeks)
I.V. or I.M. (5 weeks)

5. Reproduction Studies

Rat oral Segment I (Fertility and Reproductive Performance)

Rat I.V. Segment II (Teratology)

Rabbit I.V. Segment II (Teratology)

Rat I.V. Segment III (Perinatal and Postnatal Study)

6. Carcinogenicity Studies

Mice oral (24 months interim report)

Rat oral (24 months, interim report)

7. Mutagenicity Studies

Bacteria *S. typhimurium* (Ames) (in vitro)

Chinese hamster (V79) lung cells (in vitro)

Chromosome analysis human lymphocytes (in vitro)

Micronucleus test in mice (in vivo)

The following parenteral formulations were used in the various toxicity studies:

1. Formulation A (maleate salt)

<u>Ingredient</u>	<u>Concentration/ml</u>
Midazolam maleate	3.5 mg*
Tartaric acid	4.0 mg
Disodium edetate	0.1 mg
Sodium chloride	7.0 mg
Benzyl alcohol	0.01 ml
Sodium hydroxide (10%)	q.s. pH 3.3 + 0.1
Water	q.s. to 1 ml

*provides 2.5 mg base equivalents plus 3% excess

2. Formulation B (base, Nutley)

<u>Ingredient</u>	<u>Concentration/ml</u>
Midazolam (free base)	5.1 mg*
Disodium edetate	0.1 mg
Sodium chloride	8.0 mg
Benzyl alcohol	0.01 ml
HCl (v/v) q.s. pH 3.3 + 0.1	
Water q.s. to 1 ml	

*5.0 mg base plus 2% excess

3. Formulation C (base, Basle)

<u>Ingredient</u>	<u>Concentration/ml</u>
Midazolam (free base)	5.0 mg
Sodium chloride	5.0 mg
Benzyl alcohol	0.01 ml
HCl (25%)	4.088 mg
Sodium hydroxide (1 N)	q.s. pH 3.3 + 0.1
Water	q.s. to 1 ml

Acute Parenteral Toxicity

1. Species	Formulation	Route	Sex	LD ₅₀ (mg/kg of base equivalents)
<u>Mouse</u> (CD-1, CF-1)	A (maleate)	I.V.		34-70 ^a
		I.M.		25
	A (maleate)	I.V.	M	44 (40-47)
			F	41 (36-49)
	B (base, Nutley)	I.V.	M	42 (36-49)
			F	44 (42-46)
	C (base, Basle)	I.V.	M	43 (39-48)
		F	48 (43-53)	
	RO 5606 (impurity of Ab)	I.V.	F	> 1000
	A (maleate)	I.V.	M	86 (71-112) ^c
	RO 21-6164/001 (open ring)	I.V.	M	142 (130-154) ^c
<u>Rat</u> (CRCD)	A	I.V.		29
		I.M.		> 5
	B	I.V.		> 50
		I.M.		> 10
<u>Rabbit</u> (NZW)	A	I.V.		> 5 ^d
		I.M.		> 2.5
<u>Dog</u> (Beagle)	A	I.V.		> 10 ^e

- a) Mortality usually occurred on the day of dosing. Signs included: decreased motor activity, hypnosis, and respiratory depression.
- b) RO 5606, an impurity of the maleate formulation, was found in concentrations of less than 0.1% after 2 years storage at room temperature of the maleate salt formulation.

- c) At pH 6 or higher midazolam salts are entirely in the closed ring form while at lower pH the compound is in equilibrium between the closed and open ring forms. A reason for the decreased lethality of the open ring (RO 21-6164/001), although presumably in closed ring form at physiological pH, is that lethality was found to be volume dependent. More dilute solutions produce more toxicities and deaths. In the concurrent experiment cited the maleate salt was administered as a 1% solution, whereas the open ring compound was given as a 2% solution. (Personal communication with Dr. Pfitzer, Hoffmann La-Roche. Supporting data is presented on pages 142-143, volume 1.127).
- d) All animals survived at the dosages tested. Adverse signs were decreased motor activity and ataxia.
- e) All animals survived at the dosages tested. Adverse signs included muscle relaxation, salivation, ataxia, sedation, disoriented behavior, and emesis.

2. Venous Irritation Study in Rabbits after Injection of Midazolam Maleate or Diazepam

Procedure: New Zealand Rabbits (NZW) were infused for 1 minute into the marginal ear vein with midazolam maleate 1.0 ml (10 mg/ml H₂O), or diazepam 1.0 ml (5 mg/ml organic diluent), or 1 ml of diazepam diluent, or 1 ml of saline. Signs of vein irritation were recorded for 10 days following administration of drugs or vehicle.

Results and Conclusions:

Compound	Concentration mg/ml	Thrombosis	Edema	Erythema	
				Injection Site	Non-Inject. Site
Saline	-	0/10	0/10	0/10	0/10
Diluent for Diazepam	-	4/10	4/10	6/10	4/10
Diazepam (in Diazepam Diluent)	5	4/10	7/10	8/10	7/10
Midazolam (in Water)	10	2/20	9/20	15/20	15/20

Midazolam at twice the concentration of diazepam was found to show similar evidence of venous irritation as diazepam or its diluent. Propylene glycol, an ingredient (40% v/v) in the diazepam diluent may contribute to the venous injury (Can. Anaesth. Soc. J. 25: 50-52, 1978).

3. Venous Irritation Study in Rabbits after Injection of Midazolam Maleate or Pentobarbital

Procedure: Three male and three female NZW rabbits per group were administered by I.V. injection into the posterior marginal ear vein: a) midazolam maleate (formulation A) at doses of 0.1, 0.5, and 2.5 mg/kg; b) 20 mg/kg Nembutal; c) vehicle; d) saline; e) uninjected control. The injection volume for controls was 1 ml/kg which was equivalent to the volume used for the high dose midazolam group. All injections were given over a 2 minute period. Daily observations for adverse clinical signs and possible vein irritation were made for 2 weeks.

Results and Conclusions:

One animal at 0.1 mg/kg midazolam showed slight sedation and ataxia. At 0.5 mg/kg slight to moderate ataxia, slowed righting reflexes and slight to moderate sedation occurred. One female lost the righting reflex. Four rabbits at 2.5 mg/kg of midazolam and 4 rabbits receiving Nembutal promptly demonstrated hypnosis after injection. Additional responses included: sedation, loss of righting reflex, ataxia and eye twitching. All rabbits appeared normal within 1-3 hours after injection.

The injection sites of rabbits treated with midazolam remained essentially free of inflammation, edema, or ulceration, venous flow was preserved. One Nembutal-treated rabbit developed venous occlusion and three others exhibited slight erythema and edema of the ear.

4. Venous Irritation Study in Rabbits after Injection of Midazolam Hydrochloride or Pentobarbital

Procedure: Five NZW rabbits per sex per group were administered by I.V. injection midazolam base or Nembutal into the left ear vein and an equal volume of vehicle into the right ear vein according to the schedule:

Group I: midazolam HCl (5 mg/ml) at 0.7 mg/kg in 0.14 ml/kg.

Group II: midazolam HCl (2mg/ml) at 0.7 mg/kg in 0.35 ml/kg.

Group III: Nembutal in saline 3 mg/kg in 0.12 ml/kg

The total volume was administered in about 45 seconds. The observation period was 14 days.

Results and Conclusions: Slight erythema was observed in all groups. Venous congestion which was scored beginning on day 2 post-dosing in groups receiving midazolam and from day 1 in rabbits receiving Nembutal, showed the following distribution:

Group I - 4 midazolam sites, 2 vehicle sites;
 Group II - 1 midazolam, 1 vehicle site. Most of the congestion subsided by day 7. Edema, necrosis, or thrombosis were not observed in any group. It is concluded that midazolam base injectable produced slight irritation which was comparable to that produced by the vehicle.

5. Muscle Irritation Study in Rabbits after Injection of Midazolam Maleate

Procedure: Nine NZW rabbits were injected at separate sites into the sacrospinalis muscle with both high (1.0 ml) and lower (0.1 ml) doses of midazolam maleate (2.5 mg/ml as base equivalents). Three rabbits were each sacrificed after 34, 48, and 72 hours. The injection sites were grossly examined for swelling, edema, hemorrhage, and necrosis.

Results and Conclusions: Slight hemorrhage was observed at the 0.1 injection sites. The hemorrhage was more pronounced at the 1.0 ml injection site. Necrosis was found at 2 of the 0.1 ml sites and 4 of the 1.0 ml sites.

6. Muscle Irritation Study in Rabbits after Injection of Midazolam Hydrochloride

Procedure: Eleven NZW rabbits were each injected at separate sites into the sacrospinalis muscle with 0.1 and 1.0 ml of midazolam hydrochloride (5 mg/ml) and similar volumes of vehicle. Muscle tissue was examined grossly.

Findings:

Muscle Irritation (summary of observations at 24, 48 and 72 hours)^a

	Edema	Hemorrhage	Necrosis
Midazolam 0.1 ml	non-irritating	v. slight	well defined
Vehicle	non-irritating	v. slight	non-irritating
Midazolam 1.0 ml	v. slight	moderate	moderate
Vehicle	non-irritating	well-defined	non-irritating

* Irritation when observed tended to be of the same intensity at all time points examined.

Conclusion: Dose-related muscle irritation appeared to be due to midazolam HCl. Similar results were found with the maleate salt.

7. Venous Irritation Study in Dogs after Injection of Midazolam Maleate

Procedure: Three beagle dogs were administered by I.V. injection 0.5 mg/kg (0.2 ml/kg) of midazolam maleate and another 3 dogs were injected with vehicle (0.2 ml/kg).

Results and Conclusions: Pharmacological effects of muscle relaxation, salivation, ataxia, loss of placing reflex, dazed and disoriented behavior, and sedation were reported after midazolam treatment. Head shaking and licking were observed in some placebo-treated dogs. No evidence of hemolysis or irritation was observed 24 hours post-dosing.

8. Venous Irritation Study in Dogs after Injection of Midazolam Hydrochloride

Procedure: Two male and two female beagle dogs were administered by I.V. injection 0.7 mg/kg (0.7 ml/kg) of midazolam hydrochloride or saline (0.7 ml/kg) over a period of 30 seconds. Blood was drawn prior to and at 1 minute post-dosing. A 10 day observation period followed.

Results and Conclusions: No evidence of hemolysis or venous irritation was observed for any dog. All midazolam-treated dogs exhibited decreased motor activity, dazed appearance and moderate ataxia shortly after dosing.

Pyramiding Dose Toxicity Study of Midazolam Maleate in Dogs after Intramuscular Injection

Test Compound: Midazolam maleate (Formulation A, 2.5 mg/ml as the base equivalent); lot no. C104037-01. Saline, lot no. C105928-01.

Number of Dogs: 2M and 2F for test compound and for placebo control

Initial Weight: 7-9.7 kg

Route: I.M. into the thigh muscle of the hind leg.

Dosage: Midazolam at 0.01 (0.025 mg/kg) and 0.03 (0.075 mg/kg) ml/kg on Wednesday and Friday of the first week. Then 0.1 (0.25 mg/kg) and 0.3 (0.75 mg/kg) ml/kg on Monday and Wednesday of the 2nd week.

Duration of Study: Fourteen days after the final dose

Parameters: The injection site was grossly examined for signs of irritation for 24 hours post dosing. Clinical signs and food consumption evaluated throughout study; hematology (Ht. Hg., total and differential WBC) seven days pre-treatment and 24 hours after the final dose; clinical chemistry (BUN, SGOT, SGPT, SAP, and glucose) at baseline, 24 hours after 0.1 ml/kg and 1, 7, 14 days after 0.3 ml/kg.

Results: Erythema was observed at the injection site in 1 dog receiving lowest dose 0.01 ml/kg. BUN was elevated 1 and 7 days after 0.1 and 0.3 ml/kg, respectively. Various elevations in SAP and glucose in both midazolam and placebo-treated dogs when compared to baseline values.

Conclusion: No consistent toxicity was observed in midazolam-treated dogs.

Subchronic Toxicity Studies of Midazolam

1. Rats (I.M.)

Study Number: 36063

Testing Laboratory: Hoffmann La-Roche, Nutley, New Jersey

Duration: 2 weeks

Test Compounds: a) Midazolam base (formulation B, Nutley), lot no. C114351-01; b) Vehicle, lot no. C 111770-01

Number of Rats: 12 CRCD rats/sex/group

Initial Body Weight: Males 250 g; Females 155 g.

Route of Administration: I.M. into the posterior muscles of both legs

Dosage Levels: Saline control, vehicle control, midazolam at 0.5, 1.6, 5.0mg/kg/day. All treatment groups received a volume of 1 ml/kg/day.

Parameters: Clinical signs and body weight (daily); food consumption (week), ophthalmic and neurological examination (pretreatment and at term); hematology (Ht, Hg, coagulation time, RBC (total and differential) pretreatment and term; serum chemistry (glucose, SAP, SGPT, SGOT, BUN, t. bilirubin, cholesterol, t. CPK, t. protein) at term; urinalysis (S.G., pH, glucose, albumin, ketones, bilirubin, blood, microscopic examination of sediment) overnight sample before term; gross pathology on all rats; organ weights (heart, lungs, liver, kidneys, spleen, brain, testes, ovaries, uterus, adrenals, thyroid (fixed), pituitary (fixed); histopathology (organs from saline control and HD groups and muscle tissue from injection sites of all groups).

Results:

Body Weight: Slight reduction mean weight HDM (about 5%) when compared to saline control.

Food consumption: Various small reductions in food consumption for vehicle and drug treatment groups when compared to saline control.

Clinical Signs: Dose related transient pharmacological signs of CNS depression in drug-treated groups.

Gross Pathology: Dose-related increased incidence of hemorrhage at the injection sites in MD and HD rats.

Histopathology: Moderate to severe chronic active myositis in most rats from all drug-treated groups. This involved myodegeneration, myonecrosis, focal hemorrhage and mixed inflammatory cell infiltration. Slight myositis were also observed in 16/24 rats in the vehicle control and 5/24 rats in the saline control group.

Summary and Conclusion: Daily I.M. injections of midazolam for two weeks resulted in the expected pharmacological signs of CNS depression. All drug dosages tested caused focal active myositis which was more severe than that produced by the vehicle control. The lowest drug dosage tested, 0.5 mg/kg/day (roughly 6X the suggested human I.M. dose) produced the same kind of lesions at the injection sites but when compared to damage at higher dosages less tissue was involved.

It is concluded that midazolam administered to rats daily by I.M. injection for 2 weeks at dosages up to 60X the suggested human dose did not cause systemic toxicities. Repeated dosing, however, caused muscle damage at the injection sites. It is doubtful that a no effect level can be reached in protocols using multiple I.M. injections since even saline injections caused myositis in some rats.

2. Rats (I.V.)

Study Number: 94153

Testing Laboratory: Hoffmann-La Roche, Basle, Switzerland

Duration: 5 weeks

Test Compound: Midazolam base (Formulation C, Basle), lot no.
PT 978817 22

Number of rats: 12 Fullensdorf albino/sex/group

Initial Body Weight: About 160 g

Route of Administration: I.V. into tail veins (Group IV, I.P. during the 5th week due to swollen veins)

Dosage Levels:

- Group I, control (saline 1.2 ml/kg)
- Group II, 1 mg/kg/day (0.2 ml/kg)
- Group III, 2.5 mg/kg/day (0.5 ml/kg)
- Group IV, 6 mg/kg/day (1.2 ml/kg)

Parameters: Clinical signs (daily); body weight (3-7X/Week); ophthalmic examination (term); hematology 6 rats/sex/group (RBC, Hg, platelets, WBC and differential, reticulocytes-control and HD only) weeks 2 and 5. serum chemistry 6 rats/sex group (SGOT, SGPT, SAP, bilirubin, BUN, glucose, cholesterol, sodium, potassium) weeks 2 and 5, and total protein and electrophoresis at week 5; urinalysis 6 rats/sex/group (volume, SG, pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, nitrite) at weeks 2 and 5; organ weights (adrenals, brain, heart, pituitary, kidneys, liver, lungs, ovaries, prostate, spleen, testes, thyroid, uterus); histopathology 6 rats/sex/group I and IV.

Results:

Body weight: Slight decrease in mean body weight (< 10%) in MD and HD M when compared to control

Clinical signs: Sedation and ataxia (transient) and acute sensitivity to noise in HD group.

Hematology: Slight increase in WBC in some rats of various dosing groups including controls.

Serum chemistry: High SGOT and SGPT values in 1HDF at week 2 (i.e. >300 μ /l vs. 30 μ /l which is within the normal range). This F not examined in week 5 since alternating rats were examined at the 2 time periods. Slight reduction (5%) in total protein in HDM at week 5.

Gross Pathology: Not done,

Histopathology: Tail veins not examined

Summary and Conclusions:

Except for the expected pharmacological signs of midazolam no evidence of consistent systemic toxicity was observed after 5 weeks of treatment. The elevated WBC count in some rats of all groups was probably due to irritation of the tail tissue. All rats in the C, LD, MD were treated via the tail veins throughout the study; however, due to swollen veins most HD rats were administered midazolam by the I.P. route during the 5th week of the study.

3. Rabbits (I.V.)

Study Number: 30664

Testing Laboratory: Hoffmann-La Roche, Nutley, New Jersey

Duration: Two weeks

Test Compound: Midazolam Maleate (Formulation A)
lot number: 3 P2278
Placebo lot number: P3P-2280

Number of Rabbits: 4 NZW/sex/group

Initial Body Weight: Males 3.3 kg
Females 3.5 kg

Route of Administration: I.V. into the ear veins delivered between 45 seconds and 2 minutes

Dosage Levels: Midazolam base equivalent at 0.1, 0.5, and 2.5 mg/kg/day (injection volumes of 0.04, 0.2, and 1.0 ml/kg respectively). Placebo volume at 1.0 ml/kg. Injections were not given to a separate group of 8 rabbits.

Parameters: Clinical signs (daily); body weight (weekly); ophthalmic and neurologic examinations (pre-study and term); hematology (Hg, Ht, WBC total and differential, prothrombin and coagulation time) pre-study and term; serum chemistry (glucose, SAP, SGPT, SGOT, BUN) pre-study and term; urinalysis (S.G., pH, glucose, protein, ketones, bilirubin, blood, microscopic) pre-study and term; gross pathology; organ weights (heart, lungs, liver, kidney, spleen, brain, ovaries, testes, uterus, prostate, thyroid, adrenals, pituitary); histopathology.

Results:

Observed Effects:

Injection sites of rabbits for all groups showed focal venous occlusion, occasional clots and focal hemorrhages. Occasional extravasation and necrosis of tissue adjacent to the injection site were seen in high dose and placebo groups.

Hypnosis occurred at 2.5 mg/kg only. Sedation, loss of righting reflex, ataxia, muscular relaxation, rapid and shallow respiration and muscular twitching occurred at 2.5 and 0.5 mg/kg levels. Very slight sedation was noted at 0.1 mg/kg. These responses occurred in a dose-related manner that diminished somewhat in degree or duration over the treatment period.

Mortality:

One LD male after cardiac puncture for blood collection.

Body Weight:

Slight mean weight loss (6%) in the HD group. MD rabbits maintained their original weight, while LD and control rabbits showed a mean weight gain of 3-4%

Serum Chemistry:

Values were similar to control values except for a high average value for glucose in the high dose group, which was due to the elevation in a single male. Reason for this high individual value is not known. Also the mean BUN value was significantly lower for high dose group compared to control group.

Organ Weights:

In the HD rabbits the mean liver weight (absolute and relative) was decreased about 15% when compared to liver weight of placebo and uninjected controls.

Gross Pathology:

Principal changes were seen at the injection sites in the ears and thorax. In the ear, focal hemorrhage, soft tissue induration and necrosis were seen primarily in the high dose and placebo groups; lesser focal changes were seen in the mid and low dose groups. In some animals the heart and adjacent mediastinal and pulmonary tissues were the site of focal hemorrhage and inflammation consequent to repeated cardiac punctures.

Histopathology:

Focal lesions were seen at the injection sites that included thrombi in vessels, hemorrhage, focal necrosis about the site and ulceration of the skin. Extensive changes in the hearts of some animals were associated with cardiac puncture. Lesions in the lung included a focal arterial inflammation that was dose dependent but also occurred in two uninjected control animals. Special staining and observations of the pulmonary arteries did not show focal mural destruction or deformity of these arteries. Inflammatory lesions in the central nervous system occurred in 3 low dose, 2 mid dose, 1 high dose, 4 placebo and 3 uninjected controls.

Discussion:

The histological changes in the lungs of rabbits treated with midazolam was described as focal acute inflammation of branches of the pulmonary arteries. In some instances the change was localized to branches of the pulmonary arteries and included peribronchial lymphoid aggregates. In other cases the arterial inflammatory change was a part of interstitial pneumonia. In several other instances the arterial inflammation occurred in arteries not adjacent to lymphoid or inflammatory foci. In animals of the 0.1 mg/kg/day dose group, the vessels showing focal inflammatory change were small and these vessels were located peripherally in the lung. Examination of pulmonary vessels for emboli and thrombi revealed very few of these. One of the acute inflammatory foci surrounding an artery occurred within a hemorrhagic, peripheral pulmonic lesion having the configuration and character of an infarct, no thrombus was identified in this case. None of the arteries with focal acute inflammatory change showed any significant degree of mural destruction, deformity, or

obstruction of the lumen of the vessel. Elastic tissue stained sections of the lung confirmed the normal architectural arrangement of the elastic laminae of the arteries and in most areas the elastic elements of the alveolar walls. Similar arterial lesions were not observed in other organs or tissues of any rabbit.

The vascular inflammation appeared to be non-specific but could have resulted from:

- 1) emboli from the ear vein
- 2) direct drug induced toxic changes
- 3) hypersensitivity to the drug or drug-induced antigens
- 4) "spontaneous" vasculitis of unknown etiology

(The above are views expressed by the manufacturer's consultant, Dr. B.M. Wagner, Director of Laboratories, Overlook Hospital, Summit, New Jersey)

In order to investigate the vascular inflammation further, the following two additional rabbit studies number 29986 and 31955 were conducted.

Study Number: 29986

Testing Laboratory: Hoffmann-La Roche, Nutley, New Jersey

Duration: Two weeks of treatment; one half of the rabbits were sacrificed 2 weeks after last injection and the remaining rabbits were sacrificed 3 months after the final injection.

Test Compound: Midazolam Maleate (Formulation A)
lot number 3P-2328; placebo
lot number 3P-2279

Number of Rabbits: 12 NZW/group (all males except for 1 female at the 0.5 dose level)

Initial Body Weight: 3.3 kg

Route of Administration: I.V. into the marginal ear veins of alternative ears in the mornings of Monday, Wednesday, Friday of each week for 2 weeks.

Dosage Levels: Midazolam base equivalents at 0.1, 0.5, and 2.5 mg/kg (0.04, 0.2, and 1 ml/kg, respectively). Placebo vehicle at 1.0 ml/kg. Saline at 1.0 ml/kg. Nembutal at 20 mg/kg in a volume of 0.4 ml/kg/day. A noninjected control group.

Parameters: Clinical signs, irritation of tissue at the injection sites were observed daily for 32 days. Rabbits, with persistent ear changes were observed for 58 days. All other rabbits were examined weekly. Body weights were measured weekly. Gross pathology on all rabbits; one half 10-12 days after the last injection and the remaining rabbits at 3 months post-dosing. Organ weights (heart, lungs, liver, kidneys, spleen, brain, testes, prostate, ovaries, uterus, thyroid, adrenal, and pituitary). Histopathology on all rabbits.

Results:

Mortality: 3 rabbits, 1 vehicle control, 1 in the Nembutal group, and 1 in the HD midazolam group.

Observed Effects: Erythema and ecchymosis in areas of injection in some rabbits of all injected groups. Rabbits exhibiting venous occlusions were 4/12 in the HD midazolam group and 12/12 in the Nembutal group. Adverse responses at the injection site were also more severe with Nembutal than with midazolam, the former drug produced sloughing and scab formation, and an exudate was seen occasionally.

Pharmacological signs of ataxia, impaired righting reflexes, and sedation were observed in most rabbits after midazolam injection. These effects and their duration were slight in the LD group. Nembutal produced muscle relaxation, ataxia, abnormal eye movements and sedation. Vehicle, saline, and uninjected controls were asymptomatic.

Body Weight: Slight (less than 5%) decrease in HD midazolam group during the treatment period. A similar decrease from control values was observed for the Nembutal group during the first week of treatment.

Histopathology: At 10-12 days after the last injection 1/6 rabbits treated with midazolam had a thrombus in an ear vein while 2/5 Nembutal-treated rabbits showed ear vein thromboses, evidence of necrosis, inflammation and scar tissue.

At the 3 month sacrifice, no vascular lesions were found in the ears or any other organ

A variety of random inflammatory lesions were noted in lungs, kidneys, liver, urinary bladder or brain of some rabbits in each group. There was no dose-response or indication that the histopathological lesions were related to midazolam or the other treatments used.

Evaluation: The results of this test indicate that the focal, pulmonary arteritis observed in study number 30664 is not midazolam related as regards direct drug toxicity or drug-related hypersensitivity.

Study Number: 31955

Testing Laboratory: Hoffman-La Roche, Nutley, New Jersey

Duration: Two weeks of treatment. All rabbits sacrificed nineteen weeks after the last injection.

Test Compound: Midazolam maleate (Formulation A), lot number 3 P-2328;

Vehicle lot number 3 P-2279

Number of Rabbits: 4 NZW/sex/group

Initial Body Weight: Males, 3.0 kg
Females, 3.2 kg

Route of

Administration: I.V. into the marginal ear veins of alternate ears daily for 2 weeks.

Dosage levels: Midazolam at 0.1, 0.5 and 2.5 mg/kg/day (0.04, 0.2, and 1.0 ml/kg, respectively); vehicle control at 1.0 ml/kg, respectively); vehicle control at 1.0 ml/kg, respectively); vehicle control at 1.0 ml/kg; saline control at 1.0 ml/kg; Nembutal at 20 mg/kg for 2 days then 15 mg/kg/day (0.3 ml/kg) for remaining treatment days. Uninjected controls.

Parameters: Clinical signs and tissue at injection sites (daily for first 30 days and then weekly); body weight (weekly); gross pathology of cervical, thoracic, abdominal organs, and of pituitary, brain and spinal cord; organ weight (heart, lungs, liver, prostate, thyroid, adrenals, pituitary); histopathology of lungs.

Results:

Mortality: Two Nembutal-treated rabbits

Clinical signs: Dose-related erythema and ecchymosis was observed at the injection site of treated rabbits. Venous occlusion occurred primarily in MD and HD midazolam groups and in the Nembutal group. Scar tissue and sloughing was noticed in 3/3 HD midazolam rabbits and in 6/6 rabbits treated with Nembutal. Sedation, loss of righting reflexes and abnormal eye movements were noted in the MD and HD midazolam rabbits. These effects were judged to be more severe in the Nembutal-treated group.

Body Weight: Dose-related decrease in body weight when compared to control in MD (6%) and HD (10%) groups during the 2 week treatment period. The body weight of Nembutal-treated rabbits was similar to control.

Histopathology: There were no drug-related changes in lungs of the rabbits in this study.

Discussion and Conclusion: A previous study (no. 30664) indicated focal arterial inflammatory changes in the lungs of rabbits after 2 weeks of I.V. injections of midazolam. An additional study (no. 29986) and the present study did not show evidence of drug induced pulmonary arteritis. The vasculitis, therefore, does not appear to be the result of direct drug toxicity or the result of hypersensitivity reactions to the drug. However, Dr. B.M. Wagner, the manufacturer's consultant states it is not possible to exclude the role of venous emboli from the injected ear veins as the cause for the lung arteritis observed in study no. 30664.

4. Dogs (I.M.)

Study Number: 35277

Testing Laboratory: Hoffmann-La Roche, Nutley, New Jersey

Duration: 2 weeks

Test Compounds: Midazolam (Formulation B, 5 mg/ml of base equivalents)
lot number C 114351-01
Vehicle, lot number C111770-01
Saline

Number of Dogs: 3 Beagles/sex/group

Initial Body Weights: Males 8.2 kg
Females 8.1 kg

Route of Administration: I.M. injection into the posterior thigh muscle. The volume injected for the high dose, vehicle and saline groups was divided into two parts and injected into both hind legs each day.

Dosage Levels: Midazolam at 0.3, 1.0 and 3.0 mg/kg/day (0.06, 0.2, and 0.6 ml/kg, respectively). Vehicle and saline were administered at 0.6 ml/kg/day.

Parameters: Clinical signs (daily); body weight (weekly). Prestudy and term: neurological and ophthalmic examination; EKG; hematology (Ht, Hg, WBC total and differential, prothrombin and coagulation time) serum chemistry (glucose, SAP, SGOT, SGPT, BUN, total protein, total cholesterol, bilirubin, CPK); urinalysis (ph, S.G., glucose, albumin, ketones, bilirubin, blood, microscopic examination of sediment); gross pathology; organ weights (heart, lungs, liver, kidneys, spleen, brain, ovaries, testes, uterus, prostate, thyroid, adrenal, pituitary); histopathology (HD and saline-treated dogs plus prostate and testes and injection sites of all dogs).

Results:

Clinical signs: There were dose-related pharmacological signs in MD and HD dogs consisting of ataxia, decreased activity and dazed appearance which were transient and disappeared within 2 hours after dosing. A single instance of ataxia occurred in 1 LD dog. Behavioral changes, also dose-related, included unusual barking, nipping, and excitement. Most unusual behaviors occurred in MD and HD dogs but a few isolated instances also were observed in the low dose group.

Serum Chemistry: In the HD group mean creatinine phosphokinase levels were significantly increased (65% compared to control). Also SGPT levels were increased (75%) and SGOT (23%).

Organ weights: Absolute and relative testes weights were somewhat reduced (35%) in HD dogs without evidence of histopathological findings.

Gross pathology: Most dogs injected with drug or vehicle had edema and hemorrhage at the injection sites. Two saline-treated dogs were also affected.

Histopathology: At the injection sites, mild focal changes in the muscle consisting of necrosis, edema, hemorrhage, scarring and inflammatory cell infiltration were found in 5/6 HD, 3/6 MD, 4/6 LD, 2/6 vehicle control, and 4/6 dogs in the saline control group.

Summary and Conclusion:

The expected pharmacological signs common to benzodiazepine drugs were observed in this species. Clinical chemistry also showed elevated liver enzymes (SAP, SGPT) which are also characteristic responses in dogs to members of this drug class. The elevated serum CPK noted in the HD dogs probably resulted from local muscle damage caused by repeated injections of relatively large doses (35X the suggested human dose) of this drug.

5. Dog (I.V.)

Study Number: 30663

Testing Laboratories: Hoffmann La-Roche, Nutley, New Jersey

Duration: 2 weeks

Test Compound: Midazolam maleate (Formulation A),
lot number 3P-2278
Vehicle, lot number 3P-2280

Number of Dogs: 3 Beagles/sex/group

Average Body Weights: Males, 12.6 kg, Females 9.0 kg

Route of Administration: I.V. injections into the cephalic vein of alternative forelimbs

Dosage Levels: Midazolam at 0.1, 0.5, and 2.5 mg/kg/day (injection volumes of 0.04, 0.2, 1.0 ml/kg, respectively). Vehicle at 1.0 ml/kg. Uninjected controls.

Parameters: Clinical Signs (daily); body weights (weekly). Prior to and at end of study: Ophthalmic examination, hematology (Hg, Ht, WBC and differential, prothrombin and coagulation time); Clinical chemistry (glucose, SAP, SGOT, SGPT, BUN); urinalysis (S.G., pH, glucose, protein, ketones, bilirubin, blood, microscopic examination of urinary sediment). Gross pathology; organ weights (heart, lungs, liver, kidneys, spleen, brain, ovaries, testes, uterus, prostate, thyroid, adrenals, pituitary); histopathology.

Results:

Clinical signs:

The injection sites were free of inflammation, edema or ulceration with the exception of slight transient edema of one high dose male on day 7 only.

At 0.1 mg/kg slight ataxia, hyperactivity, and a biting and chewing reaction was observed with onset occurring immediately after dosing and lasting up to 20 minutes.

At 0.5 mg/kg the above effects lasted up to 30 minutes. All 6 dogs exhibited muscular relaxation of the limbs and incoordination immediately after the first daily injection, but rarely thereafter. Occasional hyperactivity and prominence of small conjunctival blood vessels were noted in several animals.

At 2.5 mg/kg all of the above effects were observed plus sedation and occasional retching and emesis. Reactions usually lasted up to one hour after injection and diminished to an overall duration of no more than 30 minutes by the end of the second week of study.

Body weight:

At 2.5 mg/kg a slight decrease (0.1 kg) occurred over the 2 week treatment period.

Gross Pathology

Injection sites showed no detectable swelling or necrosis of overlying skin and soft tissue. Dissection of the site frequently revealed extravasation of blood.

Histopathology

Dose-related pathological venous changes including phlebitis, sclerosis, hyperplasia, thrombosis principally in MD and HD groups. Fibrosis was observed in LD and vehicle control groups.

Summary and Conclusion:

A two week intravenous study in dogs (0.1, 0.5 and 2.5 mg/kg) produced dose dependent transient effects, lasting up to an hour, consisting of altered behavior and neurologic function. Histologic observations revealed focal changes (hyperplasia, thrombosis, sclerosis and fibrosis) at the sites of repeated injection. These venous changes were dose-related and occurred primarily in dogs receiving injections of 0.5 mg/kg and 2.5 mg/kg. Venous changes (fibrosis) in the low dose group (0.1 mg/kg) were similar to changes found in dogs injected with the vehicle.

6. Dog (I.V. and I.M.)

Study number: 94152

Testing laboratory: Hoffmann-La Roche, Basle, Switzerland

Duration: 5 weeks

Test Compound: Midazolam base (Formulation C),
lot number OP PT 9788 H22Average Body Weights: Males 12.0-15.2 kg
(Swiss Beagle) Females 9.8-13.4 kg

Route of

Administration: I.V. and I.M. (specific sites not given)

Dosage Levels:

Group	Midazolam mg/kg/day	Midazolam ml/kg/day		Dogs	
				M	F
I	0	1.2	saline i.v.	3	3
II	1	0.2	i.v.	3	3
IIIa	2.5	0.5	i.v.	2	2
IIIb	2.5	0.5	i.m.	2	2
IV	6	1.2	i.v.	3	3

Parameters: Clinical signs and body weight (daily); hematology (RBC, Hg., WBC and differential reticulocytes, platelets) pretreatment, 2 and 5 weeks; serum chemistry (SGOT, SGPT, SAP, bilirubin, BUN, glucose, electrolytes, cholesterol; t. protein electrophoresis [0 and 5 weeks] pretreatment, 2 and 5 weeks; urinalysis (S.G., pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, nitrites, sediment) at 2 and 5 weeks; EKG (all groups week 0 and groups I and IV at week 5); organ weights (adrenals, brain, heart, pituitary, kidneys, liver, lungs, ovaries, prostate, spleen, testes, thyroid/parathyroid, uterus); histopathology.

Results:

Clinical Signs: Dose-dependent sedation, ataxia which diminished with time and duration of treatment. Mild effects in MD and LD dogs after 1 week of treatment.

Serum Chemistry: When compared to saline controls, there was a slight increase in SAP in most treated groups at 2 and 5 weeks. There was a slight increase in mean SGOT at week 2 in the group receiving 2.5 mg/kg by I.M. injection. One dog exhibited a large increase in SGPT (group Iia) at week 2 but this parameter was within normal limits at week 5.

Histopathology: Inflammation was observed at the I.M. injection sites of dogs receiving 2.5 mg/kg. One dog in this group also had focal myositis and necrosis. After repeated I.V. injections some dogs in all groups exhibited phlebitis and periphlebitis with hematomas. Drug-treated groups were affected more severely. The number of dogs affected were 2/6 controls, 3/6 LD, 2/4 MD and 6/6 HD. One HD dog (6 mg/kg) also had venous obliteration.

Summary and Evaluation:

The expected CNS pharmacological signs characteristic of benzodiazepine drugs were seen. No consistent systemic abnormalities were noted with the exception of transient and/or slight to moderate elevation in liver enzymes. Transient elevations of this type have been noted previously with other benzodiazepine drugs in dogs. The pathological changes observed were limited to the injection sites. Dose related myositis and muscle degeneration occurred after IM injections of midazolam and more severe phlebitis, periphlebitis and hematomas were observed in dogs injected I.V. with midazolam when compared to the saline-injected control dogs.

Reproduction Studies

J. Fertility and Reproduction Study in Rats (Segment I)

Study Number: 32713

Testing Laboratory: Hoffmann-Laloché, Nutley, New Jersey

**Test Compounds: Midazolam maleate (formulation A)
lot number C-10403701; vehicle lot number and C-1055801 and
C-10276701**

Number of Rats: 24 male and 24 female CRCD rats/group

Initial Age: About 110 days old

**Route of
Administration:**

Oral intubation (Note: Parenteral administration was considered impractical due to the long term dosing requirements of the Segment I reproduction study. The sponsor in a dose-finding study determined the oral doses of midazolam maleate injectable substance which could be satisfactory replacements for I.V. doses. It was found that 16 mg/kg orally produced similar clinical signs and blood levels (AUC) as did an I.V. dose of 4 mg/kg. On this basis, the high oral dose selected for the Segment I study was 16 mg/kg.

Dosage Levels:

Midazolam maleate at 1, 4, 16mg/kg/day in a volume of 6.4 ml/kg. Vehicle (formulation without midazolam) at 6.4 ml/kg/day.

Duration of treatment:

Males were treated for 62 days prior to mating and throughout the mating period (2 weeks). Females were dosed 14 days prior to mating and until sacrifice at day 13 of gestation (Group A-12 females) or until day 21 of lactation (Group B-12 females).

Parameters:

Male and female body weights initially and at weekly intervals. Females were also weighed on gestation day 0, 7, 14, and 21 and lactation days 0

(delivery), 7, 14, and 21 (weaning). On day 13 of gestation, the number of corpora lutea, embryos, and resorptions were recorded. The remaining dams (about 8-12 in each group) delivered their young at term and the litters were examined for live and still born offspring. The pups were examined for external malformations, counted and weighed at birth, and on day 4 and 21 of lactation. The study was terminated at weaning of the pups. The dams were examined for implantation sites, and 1/3 of each litter was examined for visceral malformations. The heart, liver and kidneys of these pups were also weighed.

Results and Summary:

Parental effects: Dose-related pharmacological signs which included ataxia. Similar effects were observed in both sexes. Average body weight of dams receiving the low dose (1 mg/kg/day) were slightly higher (6%) during the latter part of the lactational period.

Litter effects: Adverse effects were not noted on day 13 of gestation. A slight decrease (8%) in the mean relative heart weight was observed in high dose female pups when compared to controls but this was not significantly different when compared to low-dose female pups. This small difference is not likely to be biologically significant.

Conclusion:

Midazolam maleate injectable formulation administered by gavage to male and female rats at doses up to 16 mg/kg/day does not have adverse effects on reproduction parameters, pregnancy, or the offspring of these pregnancies.

2. Teratology Studies in Rats (Segment II)

Study Number: 31498

Testing Laboratory: Hoffmann-La Roche, Nutley, New Jersey

Testing Compounds: Midazolam maleate (formulation A)
lot no. C-100756-01.
Vehicle, lot no. C-10276701

Number of rats: 30 female Charles River CD rats/group
60 males (untreated)

Initial Age: Adult males, females about 110 days old

Route of

Administration: I.V. into the caudal vein at a rate of about 2 ± 0.5 ml/min.

Dosage Levels: Midazolam maleate as the base equivalent at 0.2, 1.0 and 4.0 mg/kg/day in a volume of 1.6 ml/kg/day. Vehicle at 1.6 ml/kg/day. Untreated controls.

Duration of treatment:

Gestation days 7 through 15 (day 0 being the day a copulation plug was found). About 20 females per group for C-section on day 21. Ten females/group were allowed to deliver and wean their young.

Parameters:

All female body weights were recorded on days 0, 7, 11, 15, 21 of gestation. For groups that weaned their young, body weights were recorded on the day of parturition, day 7, 14 and 21 (weaning). Implantation, resorption sites, and corpora lutea were counted. Fetuses were weighed and examined for external abnormalities. About 1/3 were examined for soft tissue anomalies and the rest for skeletal malformations. For the group allowed to deliver, the litters were examined for external abnormalities, weighed individually at birth and on days 4, 14 and 21 of lactation. For statistical tests the litter was considered to be the unit of treatment.

Maternal Effects: All drug treated females showed slight to moderate ataxia lasting 15-30 minutes after injection. Decreased weight gain (about 5%) was recorded on days 11-15 in the high dose group when compared to control.

Fetal Effects: Teratology: no adverse drug related effects. There was a dose-related increase in post-implantation loss in pups from females allowed to deliver: vehicle control 4%, LD 9%, MD 12%, HD 16% (includes dead pups, resorbed fetuses and cannibalized pups). Note: Historical control (Segment I studies) indicated post-implantation losses over a range of 3-15%.

Summary of Results

Treatment groups (mg/kg)	Untreated Control	Vehicle	0.2	1.0	4.0
Pregnant rats at term (no.)	20	19	18	20	18
Viable fetuses (no.)	253	234	229	272	235
Average litter size (no.)	126 ± .6	12.3 ± .6	12.7 ± .7	13.6 ± .5	13.1 ± .7
Resorptions (%) (no. resorptions/ no. implantations)	7.3	6.0	6.9	6.2	7.8
External abnormalities (no.)	0	0	1	0	0
Visceral abnormalities (no.) (no. examined)	1 87	0 80	2 75	1 92	0 81
Skeletal abnormalities (no.) (no examined)	0 166	0 154	0 154	0 180	0 154
Skeletal variations (no. examined)	53 166	53 154	51 154	50 180	56 154

Evaluation:

In the Segment II teratology study in rats there was no evidence of drug induced fetal abnormalities. The increase in post-implantation loss in litters allowed to deliver from the MD and HD groups does not appear drug related because losses were within the historical control incidence and dose-related post-implantation loss was not evident in the the teratology phase of this study.

3. Rabbit Teratology Study (Segment II)

Study Number: 31496

Testing Laboratory: Hoffmann-La-Roche, Nutley, New Jersey

Test Compounds: Midazolam maleate (formulation A)
lot no. C-100756-01.
Vehicle lot no. C-102767-01

Number of Rabbits: 15 females NZW per drug groups
30 females for vehicle control group
15 females for non-treated control group

Initial Weight: About 4.3 kg

Route of Administration:

I.V. into the ear vein at a rate approximately 2 ± 0.5 ml/minute

Dosage Levels: Midazolam maleate as the base equivalent at 0.2, 0.6 and 2.0 mg/kg/day; vehicle at 0.8 ml/kg/day.

Duration of Treatment:

Daily from day 7 to day 18 of gestation (day 0 being the first 24 hours after observed mating).

Parameters:

Observation of all females, 1 hour after dosing and at the time of weighing. Body weights reported for days 0, 7, 14, 21 and 29 of gestation. Viable fetuses, resorptions, and corpora lutea counted. All fetuses examined for external malformations, sexed, weighed and sized. Viable fetuses incubated for 24 hours to determine survivability. All pups examined for visceral and skeletal abnormalities. For statistical analysis the litter was considered the unit of treatment.

Maternal Effects: Dose-related ataxia and sedation. The low dose group was asymptomatic 60 minutes post-dosing. The mid dose group showed few effects and the high dose group showed marked effects even at 60 minutes after dosing. These signs were generally absent after two hours. Maternal body weight was not effected by drug treatment.

Fetal Effects: The resorption rate was greater in the high dose group (17.4%) but not statistically different when compared to other groups: -untreated- control (11.2%), vehicle (10%), low dose (13.8%) and mid-dose (8.2%). A statistically significant increase in external abnormalities was found in the low-dose group, but without a specific syndrome of malformation and most (9) abnormal fetuses were from one litter. In this group, 9 litters of 13 showed no external abnormalities.

Treatment groups (mg/kg)	Summary of Results				
	Untreated Control	Vehicle	0.2	0.6	2.0
Pregnant rats of term (no.)	13	22	13	13	9
Viable fetuses (no.)	103	188	106	112	71
Average Litter Size (no.)	7.9 ± .5	8.5 ± .5	8.2 ± .8	8.6 ± .5	7.9 ± 1
Resorptions (%) (no. resorptions/ no. implantations)	11.2	10	13.8	8.2	17.4
External abnormalities (no.)	0	1	12*	0	0
Visceral abnormalities (no.)	0	4	2	4	1
Skeletal abnormalities (no.)	6	11	13	2	2
Abnormalities (%) (no.)	5.8 6/103	7.4 14/188	17.9 19/106	5.4 6/112	4.2 3/71

*1 fetus-hyperflexion of forepaws, 1 fetus-domeshaped head, 1 fetus pes cavus, 9 fetuses (one litter)-open eyelids, cleft palate.

Evaluation: Although dose-related pharmacological signs of maternal adverse effects were observed, there was no evidence of drug-related fetal malformations. The resorption rate in the high dose group, while greater than the incidence found in the other concurrent groups, is not outside the range for spontaneous resorptions in rabbits.

4. Prenatal/Postnatal Reproduction Study in Rats (Segment III)

Study Number: 32711

Testing Laboratory: Hoffmann-La Roche, Nutley, New Jersey

Test Compound: Midazolam maleate (formulation A)
lot. no. C-100756-01; Vehicle.
lot no. C-10276701 and C-105558-01

Number of rats: 20 female CRCB rats per dose group

Initial Age: About 100 days old

Route of Administration: I.V. into the caudal vein at a rate of about 2 ± 0.5 ml/minute.

Dosage Levels:

Midazolam maleate as the base equivalent at 0.2, 1.0 and 4.0 mg/kg/day in a volume of 1.6 ml/kg/day; vehicle at 1.6 ml/kg/day; non-treated controls.

Duration of Treatment: Day 15 of gestation (finding of vaginal plug was day 0) through day 21 of lactation.

Parameters:

Female body weights were recorded on gestation day 0 and 15 and on lactation days 0 (delivery), 7, 14, and 21. Litters were examined for live and dead offspring and external abnormalities. Then pups were weighed at birth and days 4 and 21. At day 21 about 1/3 of each litter was autopsied and weights of heart, kidneys and liver were recorded. Pups that died during the study were examined for skeletal abnormalities.

Maternal Effects:

Dose-related pharmacological effects of ataxia and transient voracious behavior immediately after dosing. Slight reduction in weight gain on lactation day 0 and day 7 in the high dose group. Also a statistically significant reduction in weight gain in the mid-dose group on lactation day 7.

Litter Effects:

Summary:

Treatment groups (mg/kg)	Untreated Control	Vehicle	0.2	1.0	4.0
Litters born	17	19	17	18	18
Average litter size at birth	11.9 ± 0.6	13.4 ± 0.5	12.4 ± 0.6	12.4 ± 0.4	10.4 ± 0.9

Pups missing and presumed cannibalized	3	2	0	10	7
Lactation Index (pups alive day 21/pups at day 4)	100	98.7	100	100	100

Summary and Conclusions:

Dosages of midazolam that caused significant pharmacological effects in pregnant rats produced no consistent adverse effects in the offspring. The slight decrease from control in relative heart weight (7%) in the high dose male pups appears to correspond to the increased body weight gain of these pups. It is known that smaller litters generally weigh more than larger litters. There is no convincing evidence that the smaller litter size of the high dose group was directly related to midazolam.

Carcinogenicity Studies**1. Carcinogenicity Study in Mice**

Study Number: 35030 (Interim report)

Testing laboratory: International Research and Development Corporation
(IRDC)
Mattawan, Michigan

Duration: 24 months

Test Compound: Midazolam maleate (lot no. 0003003)

Number of Mice: 80 B₆C₃F₁/sex/group

Age at onset of dosing: About 5 weeks old, weight greater than 12 grams

Route of Administration: Mixed in food. Food analyzed for homogeneity at pretest, and weeks 1, 13, and then every 13 weeks.

Dosage Levels: Midazolam at 0, 0, 1, 9, 80 mg/kg/day

Parameters:

Clinical signs (daily with more detailed weekly observations such as masses, corneal opacities, incisor maladjustment); body weight and food consumption (weekly for the first 14 weeks, thereafter every two weeks); ophthalmoscopic examinations (pretest and at 3, 6, 12, 15, 18, 21, and 24 months); hematology: Hg, Ht, RBC, WBC, differential, platelets (in mice sacrificed at pretest, 18, and 24 months); gross pathology (all mice that died or were sacrificed); organ weights (brain, liver, kidneys, spleen and heart at 24 months); histopathology: report not completed: results reported for most organs examined at 0-18 and 18 month interim sacrifice, whereas results from only the liver have been reported for mice that died or were sacrificed at 18-24 months.

Results:

Body Weight

Higher body weight gain for mid-dose and high-dose females (mean increase from controls of about 5% and 8%, respectively).

Survival at 104 Weeks

Dose (mg/kg/day)	No. survivors/no. initiated*	
	M	F
0	57/65	50/65
0	54/65	54/66
1	50/65	52/65
9	53/65	52/65
80	38/65	55/65

* Does not include the 18 month interim sacrifice of 15 mice/sex/group

Organ Weight

A statistically significant increase was observed in mean absolute and relative liver weight of the high dose female group and the mid and high dose males.

Gross Pathology

At about 70 weeks an increased number of high dose males had a single ventral abdominal mass. This was determined to be distended urinary bladders and ureters. Since most of these mice also had inflammation and ulceration of the prepuce, the distended bladders and ureters were considered secondary to the preputial inflammation.

Liver Mass/Nodules

Dose (mg/kg)	M		F	
	(DOS)	(TS)	(DOS)	(TS)
0	2	19	2	6
0	4	18	1	8
1	4	15	1	8
9	4	20	4	10
80	7	20	6	43*

DOS - 18 to 24 months
 TS - Term (24 month sacrifice)

Histopathology

A. Primary Liver Tumors (Adenomas and Carcinomas¹)

Dose (mg/kg)	Female Mice (B ₆ C ₃ F ₁)				
	0	0	1	9	80
<u>0-18 Months</u>					
No. of mice	20	22	15	19	17
No with tumors (%)	1 (5)	1 (5)	2 (13)	2 (11)	8 (47) ^a
Adenoma	1		2	2	5
Carcinoma		1			3
<u>18-24 Months</u>					
No. of mice	60	58	65	61	63
No. with tumors (%)	4 (7)	5 (9)	10 (15)	9 (15)	50 (79) ²
Adenoma		2	9	5	26
Carcinoma	4	3	1	4	19

Overall Incidence

No. of mice	80	80	80	80	80
No. with tumors (%)	5 (6)	6 (8)	12 (15)	11 (14)	58 (73) ²
Adenomas	1	3	11	7	33
Carcinoma	4	3	1	4	25

- 1) A few hemangiomas also observed with no dose relationship.
- 2) Statistically increased from control. Also higher than historical controls for this strain of mouse.

Dose (mg/kg)	Male Mice (B ₆ C ₃ F ₁)				
	0	0	1	9	80
<u>0-18 Months</u>					
No. of mice	18	18	19	20	25
No. with tumors (%)	6 (33)	1 (6)	1 (5)	5 (25)	8 (32)
Adenoma	5		1	4	7
Carcinoma	1	1		1	1

18-24 Months

No. of Mice	62	62	61	60	55
No. with tumors (%)	24 (39)	30 (48)	20 (33)	24 (40)	28 (51)
Adenoma	14	15	9	6	12
Carcinoma	10	15	11	18	16

Overall Incidence

No. of mice	80	80	80	80	80
No. with tumors (%)	30 (38)	31 (39)	21 (26)	29 (36)	36 (45)
Adenomas	19	15	10	10	19
Carcinoma	11	16	11	18	17

Historical Control (Adenoma and Carcinoma (2 year studies))

	M	F
IRDC (1982)		3.3-4.3% (1,663 mice)
JNCI 62: 957 (1979)	16%	3%
JNCI 66: 1,175 (1981)	7-58% ¹	0-21% ¹
Chu/NIH NCI	20%	4%

¹ Range from 5 laboratories

Description of primary liver tumors in the present study:

Adenoma: Benign neoplasm characterized by proliferating homogenous cells most of which have well-defined borders. The cells are generally well-differentiated. Many tumors show focal to generalized fatty degeneration.

Carcinoma: Often massive in size with ill-defined borders. Contain large round cells with large hyperchromatic nuclei and a low mitotic index. Some tumors display a trabecular pattern with sinusoidal dilatation and large mononuclear giant cells having hyperchromatic nuclei. These cells were found in clusters and often separated from the major mass.

B. Hepatocellular Hypertrophy

Dose (mg/kg)	Female Mice				
	0	0	1	9	80
<u>0-18 Months</u>					
No. of mice	20	22	15	19	17
No. with hypertrophy(%)	0	0	0	1 (5)	7 (41)
No. with tumors				1	7
No. without tumors				1	7
<u>18-24 Months</u>					
No. of Mice	60	58	65	61	63
No with hypertrophy(%)	0	2 (3)	0	1 (2)	32 (51)
No. with tumors					22
No. without tumors		2		1	10
<u>Overall Incidence</u>					
No. of mice	80	80	80	80	80
No with hypertrophy(%)	0	2 (3)	0	2 (3)	39 (49)
No. with tumors					22
No. without tumors		2		2	17

Dose (mg/kg)	Male Mice				
	0	0	1	9	80
<u>0-18 Months</u>					
No. of mice	18	18	19	20	25
No. with hypertrophy (%)	0	1 (6)	0	0	18 (72)
No. with tumors ¹					3
No. without tumors		1			15
<u>18-24 Months</u>					
No. of Mice	62	62	61	60	55
No. with hypertrophy (%)	3 (5)	3 (5)	5 (8)	8 (13)	39 (71)
No. with tumors ¹					19
No. without tumors	3	3	5	8	20
<u>Overall Incidence</u>					
No. of mice	80	80	80	80	80
No. with hypertrophy (%)	3 (4)	4 (5)	5 (6)	8 (10)	57 (71)
No. with tumors ¹					22
No. without tumors	3	4	5	8	35

¹ Adenomas or carcinomas plus hypertrophy

Evaluation:

There is an increased incidence of primary liver tumors (adenomas and carcinomas) in female mice that received the high dose of 80 mg/kg/day. The increase in liver tumors is statistically significant at 18 months or longer when compared to the incidence of tumors in control female mice.

2. Carcinogenicity Study in Rats

Study Number: 35278 (Interim report, volumes 13.1 and 13.3)

Testing Laboratory: Hoffmann-LaRoche, Nutley, New Jersey

Duration: Two year oral toxicity/carcinogenicity study. (Interim report 78 weeks)

Test Compound: Midazolam maleate (lot nos. 0003001, 009011, 010071, 007110, and 0009004)

No. of rats: 90 CRSD/sex/group

Age at Onset of Dosing: 4-5 weeks old, 86 gm. males and 80 g females

Route of Administration: Mixed in food, diets were prepared weekly.

Dosage Levels: Midazolam at 0, 0, 1, 9, 80 mg/kg/day.

Parameters:

Mortality and morbidity (daily); clinical signs, body weight, food consumption (weekly); neurological examination (pre-dosing then at quarterly intervals); ophthalmologic examination (all rats pre-dosing and 10/sex/group at weeks 14, 26, 39, 52, 67, 15 sex/group at week 77); hematology: Hg, Ht, WBC and differential, coagulation time (10 rats/sex/group pre-dosing and at 11, 25, 39, 51, 66 weeks; 15/sex/group after 77 weeks); serum chemistry: glucose, SAP, SGOT, SGPT, BUN (at sacrifice); serum prolactin (rats sacrificed after 78 weeks); urinalysis: color, SG, pH, glucose, albumin, ketones, bilirubin, blood, sediment on 10/sex/group at weeks 11, 26, 39, 51, 66 and on 15 sex/group after 78 weeks); pathology: all rats that died, 10 sex/group after 26 weeks and 15/sex/group after 78 weeks); organ weights: heart, lung, liver, kidneys, adrenals, spleen, brain, testes, ovaries, uterus, thyroid (fixed), and pituitary (fixed); histopathology: the interim reports give a summary of liver histology at term (2 years). Appendix A, volume 13.1.

Results:

Mortality: (by week 78, excluding interim sacrifice on week 26 of 10/sex/group, and on week 78 of 15/sex/group).

Dose (mg/kg)	M	F
0	5	6
02	10	4
1	11	9
9	7	6
80	15	9

Body Weight

When compared to controls, high dose male body weight was slightly higher (less than 10%) from weeks 11-50; thereafter, the body weight was slightly lower (less than 10%) from weeks 71 to week 78.

High dose female body weight gain was slightly lower from weeks 7-30 and then moderately lower (20%) from weeks 50-78.

Food Consumption

Consistently higher mean food consumption (about 5-10%) in high dose males from weeks 4-78.

Serum Chemistry

BUN: Slightly increased in high dose females at 26 weeks. Two HDM (BUN: 83.2 mg/dl, 92.4 mg/dl) and 2 HDF (82.4 ng/dl and 52.5 mg/dl) were examined at 78 weeks. Histopathology showed age-related kidney changes common to this strain.

Prolactin: Mean levels were lower in HDF (65 ng/ml versus about 100 ng/ml for other groups). All female rats with higher prolactin levels 125-500 ng/ml had pituitary tumors. However, pituitary tumors were also observed in some male and female rats with prolactin levels in the normal range. No dose relationship was evident for pituitary tumors.

Urinalysis

High dose male rats had increased excretion of albumin after weeks 26, 51, 66 and 78.

Organ Weights

Relative to Control

Liver: HDM increased absolute (54%) and relative weight (46%) at week 26 and 25% and 40%, respectively, at week 78.

HDF increased absolute (38%) and relative weight (33%) at 26 weeks and 20% and 33%, respectively, at 78 weeks.

Thyroid: HDM increased absolute (25%) and relative weight (15%) at 26 weeks and 40% and 57%, respectively at 78 weeks.

HDF increased absolute (8%) and relative weight (11%) at 26 weeks and 14% and 22%, respectively, at 78 weeks.

Histopathology

Liver:

Centrilobular Hypertrophy

26 weeks	78 weeks
A11 HDM + HDF	15/15 HDM
17/20 MDM + F	12/15 HDF
	7/15 MDM
	7/15 MDF
	3/15 LDF
	1/15 LDM
	0/30 C

A. Primary Liver Tumors (adenoma and carcinoma)

Dose (mg/kg)	Female Rats				
	0	0	1	9	80
<u>0-18 Months</u>					
No. of rats	31	29	34	31	34
No. with tumors (%)	0	2 (7)	1 (3)	3 (10)	1 (3)
Adenoma		2	1	1	
Carcinoma				2	1
<u>18-24 Months</u>					
No. of rats	59	61	56	59	56
No. with tumors (%)	2 (3)	1 (2)	4 (7)	3 (5)	7 (13)
Adenoma	2	1	4	2	6
Carcinoma				1	1
<u>Overall Incidence</u>					
No. of rats	90	90	90	90	90
No. with tumors (%)	2 (2)	3 (3)	5 (6)	6 (7)	8 (9)
Adenomas	2	3	5	3	6
Carcinoma		1		3	2

Dose (mg/kg)	Male Rats				
	0	0	1	9	80
<u>0-18 Months</u>					
No. of rats	30	35	35	32	40
No. with tumors (%)	2 (7)	3 (9)	0	0	1 (3)
Adenoma	1	3			1
Carcinoma	1				1
<u>18-24 Months</u>					
No. of rats	60	55	55	58	50
No. with tumors (%)	3 (5)	7 (13)	2 (4)	3 (5)	2 (4)
Adenoma	2	4	2	2	2
Carcinoma	1	3		1	
<u>Overall Incidence</u>					
No. of rats	90	90	90	90	90
No. with tumors (%)	5 (6)	10 (11)	2 (2)	3 (3)	3 (3)
Adenomas	3	7	2	2	1
Carcinoma	2	3		1	2

B. Non-Neoplastic Liver Histopathology: Female Rats

Dose (mg/kg)	0	0	1	9	80	
<u>0-18 Months</u>						
No. of rats		31	29	34	31	34
No. hyaline hyperplasia ¹		3	2	4	4	2
Clear cell hyperplasia ¹				1		4
Centrilobular hypertrophy				3	16	31
Centrilobular fatty change					1	1
<u>18-24 Months</u>						
No. of rats		59	61	56	59	56
No. hyaline hyperplasia		17	21	22	17	22
Clear cell hyperplasia		9	4	2	9	13
Centrilobular hypertrophy				3	20	47
Centrilobular fatty change					1	13

Overall Incidence

No. of rats	90	90	90	90	90
No. hyaline hyperplasia	20	23	26	21	24
Clear cell hyperplasia	9	4	3	9	17
Centrilobular hypertrophy			6	36	78
Centrilobular fatty change				2	14

1 Modular hyperplasia either focal or multifocal

Non Neoplastic Liver Histopathology: Male Rats

Dose (mg/kg)	0	0	1	9	80

0-18 Months

No. of rats	30	35	35	32	40
No. hyaline hyperplasia ¹	4	5	2	6	2
Clear cell hyperplasia ¹	1				1
Centrilobular hyperplasia			1	19	33
Centrilobular fatty change			1		8

18-24 Months

No. of rats	60	55	55	58	50
No. hyaline hyperplasia	15	17	20	26	14
Clear cell hyperplasia	8	6	3	3	7
Centrilobular hypertrophy				31	39
Centrilobular fatty change		1		9	8

Overall Incidence

No. of rats	90	90	90	90	90
No. hyaline hyperplasia	19	22	22	32	16
Clear cell hyperplasia	9	6	3	3	8
Centrilobular hypertrophy			1	50	72
Centrilobular fatty change		1	1	9	16

Kidney: (0-18 months)

Focal Tubular Dilatation of the Cortex

Dose (mg/kg)	0		0		1		9		80	
	M	F	M	F	M	F	M	F	M	F

Number of rats affected	10/30	6/31	16/34	6/29	16/35	12/33	19/32	10/30	24/40	18/34
(%)	(33)	(19)	(47)	(21)	(46)	(36)	(59)	(33)	(60)	(56)

Evaluation:

This interim report contains the histopathological analysis of the liver after two years of continuous oral treatment with midazolam at doses of 1, 9, 80 mg/kg. Results from all other parameters are reported up to the 18 month interim sacrifice. Because the study report is not complete, only an evaluation of the liver will be made.

High dose rats, males and females, display drug-related hypertrophy and fatty changes in the centrilobular region of the liver. Primary liver tumors, adenomas and carcinomas, were not increased in male or female rats after 2 years treatment with midazolam.

Mutagenicity Studies**1. Bacteria**

Study Number: 89020

Test Compound: Midazolam maleate dissolved in distilled water

- a) Salmonella typhimurium: TA 1535, TA 1537, TA 1538, TA 98, and TA 100 with and without liver homogenate S-9 fraction prepared from male rats given 0.1% phenobarbitone in drinking water 5 days before sacrifice. Positive mutagens were not tested. (Standard Ames test).
- b) Fluctuation test: S. typhimurium, TA 1535, TA 1537 and TA 1538. Neither liver S-9 nor positive mutagenic compound were used.

Summary and Conclusions

Ames test: Midazolam maleate at concentrations of 0, 50, 100 and 500 ug/plate did not have mutagenic activity. At 750 ug/plate the test compound was toxic to the bacteria.

Fluctuation test: This test which can detect very weak mutagens (Mutation Research 65: 133-226 (1979) did not reveal mutagenic activity for midazolam maleate at concentrations up to 25 ug/ml. Higher concentrations were toxic to the bacteria.

2. Bacteria

Study Number: 122616

Test Compounds: Midazolam maleate at 0, 2, 25, and 250 ug/plate with and without S-9 liver supernatant from B6C3F1 female mice 42 days old administered midazolam 80/mg/kg/day in the diet for 8 days. Standard food without drug was given 18 hours before sacrifice. Aroclor-induced rat liver S-9 was used with known mutagens cyclophosphamide and benzopyrene.

Test bacterial strains: S. typhimurium TA 1535, TA 100, TA 1537, and TA 98 (Standard Ames test)

Results and Conclusions:

Midazolam at 250 ug/plate was at the limit of toxicity for TA 100. Therefore another experiment was conducted with 75, 150 and 200 ug/plate with TA 100. Midazolam with and without mouse liver S-9 did not exhibit mutagenic activity. The positive mutagens, cyclophosphamide and benzopyrene were mutagenic after rat S-9 activation in TA 1535, TA 100, TA 1537, and TA 98.

3. Mammalian Cells

Study Number: 96734 (Hoffmann-La Roche, Basle)

Test Compounds: Midazolam maleate in DMSO for 16 hours at 37.5, 75, 150 ug/ml without rat S-9 and for 5 hours at 37.5, 75, 150, 200, and 250 ug/ml with Aroclor-induced rat S-9. Positive controls were ethyl methanesulfonate and 2-acetyl-aminofluorene.

Test System: Chinese hamster lung cells (V79)

Results:

Incubation of cells for 16 hours with 37.5-150 mg/ml of midazolam without S-9 or for 5 hours with S-9 at 37.5-250 ug/ml did not induce mutations. Midazolam was found to be cytotoxic (cell survival 38%) at 150 ug/ml for 16 hours and at 250 ug/ml + S9 (27% cell survival). Positive mutagens induced point mutations as expected, i.e., forward mutations at the HGPRT locus resulting in 8-azaguanine resistant cells.

4. Human Lymphocytes

Study Number: 96684 (Hoffmann-La Roche, Basle)

Test Compounds and Procedures:

Midazolam maleate in saline at 10, 50, 100 ug/ml with Aroclor-induced rat liver S9 and at 5, 25, 50 ug/ml without S-9. Incubation times were two hours with S-9 and 24 hours without S-9. Positive mutagens were bleomycin sulfate 10 ug/ml in saline and cyclophosphamide (+S9) 50 ug/ml in water. The lymphocytes were prepared from a healthy 48 year old woman. A total of about 200 metaphases were scored (blinded) from each dose level.

Results:

There was no increase in chromosomal aberrations or breaks with midazolam. An increase in chromosome breaks was observed with the known mutagenic compounds.

5. Micronucleus Test in Mice (Fullensdorf Albino SPF, outbred strain, 6-8 weeks old).

Study Number: 96683 (Hoffmann-La Roche, Basle)

Test Compounds:

Midazolam maleate orally in saline at 0 (saline), 20, 400, 800 mg/kg. Procarbazine HCl was the positive control at 50 mg/kg.

Procedure:

Mice were orally administered compounds 30 and 6 hours before sacrifice of 3 males and 3 females/dose group. Four bone marrow smears were prepared from each mouse. About 2000 polychromatic erythrocytes were examined in a double blinded fashion.

Results:

Midazolam did not induce an increase in the number of micronuclei in PCE. Procarbazine caused an increase in the number of PCE micronuclei. Thus, midazolam did not produce chromosomal breaks or cause mitotic nondisjunctions under conditions of this experiment.

General Summary and Evaluation

Midazolam, an imidazobenzodiazepine, is a new chemical entity of the benzodiazepine class. Like all benzodiazepine drugs, midazolam's preclinical neuropharmacological profile demonstrates anxiolytic (anticonflict, calming effects), sedative, anticonvulsant, and muscle relaxant properties. Its range of activities, potency, and duration of action in various animal tests appears to be roughly similar to diazepam. It has high affinity in vitro for the benzodiazepine receptor in rat brain. Since midazolam salts are water soluble, its parenteral formulations are in aqueous media in contrast to currently available parenteral benzodiazepines which are soluble only in organic solvents. Hence, the parenteral form of midazolam was developed in anticipation that it would be more compatible and less irritating to tissues than other benzodiazepine drugs that require organic solvents for dissolution.

Metabolism and pharmacokinetic studies were conducted with ¹⁴C - labeled midazolam administered as a single I.V. dose to mice, rats, dogs and men. The major metabolite in all four species is the 1-hydroxymethyl compound with lesser amounts of the 4-hydroxy and the 1-hydroxymethyl-4-hydroxy analogs. Very little of the intact drug is excreted and virtually all of the metabolites in the urine are conjugated with glucuronide or sulfate. Pharmacological studies on mice indicated that the CNS activities are due to midazolam and not its metabolites. Dogs and men show a similar pharmacokinetic pattern after I.V. dosing. The elimination half-life in dogs and men is 1 and 1-2 hours, respectively. Recovery of 1-hydroxymethyl midazolam in the urine by 72 hours was about 40% of the administered dose for dogs and 40-60% for men. Placental transfer of ¹⁴C-midazolam occurs in rats; however, fetal levels of radioactivity were less than levels in maternal blood or in the placenta, which suggests slower or limited placental transfer of midazolam or its metabolites. Midazolam is highly bound (greater than 98%) in vitro to rat, dog, human plasma samples and to a human albumin solution.

Cardiovascular and respiratory parameters were measured after a single I.V. dose (range 4-20 mg/kg) of midazolam in barbiturate or chloral hydrate anesthetized dogs. Transient decreases were noted in blood pressure (25-40 mm Hg) and in the volume of inspired air (30%). Effects were not observed on myocardial performance or on ECG evaluations. Drug interaction studies were also conducted in conscious dogs administered an I.V. dose (0.15 mg/kg) of midazolam maleate alone or in combination with I.M. doses of hydroxyzine HCl (0.7 mg/kg), atropine sulfate (0.007 mg/kg) and meperidine HCl (1 mg/kg). There were slight transient decreases in blood pressure with the combination of hydroxyzine, atropine and meperidine and transient increases in blood pressure (20-30 mm Hg) with these three drugs plus midazolam or with midazolam and saline. After midazolam treatment, blood pressure returned to normal within 15 minutes.

Toxicological studies with midazolam include multi-week parenteral dosing in rats (2 weeks), rabbits (2 weeks) and dogs (2 and 5 weeks). The expected CNS pharmacological signs characteristic of benzodiazepine drugs were seen in all species. No consistent systemic abnormalities were noted with the exception of transient and/or slight to moderate elevation in liver enzymes SGPT, SGOT, and SAP in dogs. Transient elevation of serum transaminases and SAP have been noted previously with diazepam and other benzodiazepine drugs in dogs. In all species, midazolam formulation I.M. caused more severe myositis and muscle degeneration when compared to I.M. injections of vehicle or saline. Increases in serum CPK were also seen in dogs treated with high doses of midazolam (3 mg/kg for 2 weeks) and probably reflect the muscle damage seen. After I.V. injections of midazolam formulation in dogs for 5 weeks, more severe phlebitis, periphlebitis, hematomas were also observed when compared to vehicle or saline treated dogs. Thus, repeated I.M. or I.V. injections for two weeks or more with midazolam formulations causes greater muscle or venous pathology in dogs than vehicle or saline injections.

Reproduction studies were conducted in Charles River Sprague-Dawley rats and New Zealand White rabbits. A parenteral formulation of midazolam was administered by gavage in the segment I study in rats because long term I.V. or I.M. dosing is not possible due to the probable severe local irritation in this species. The high dose was 16 mg/kg/day which was selected because as a single oral dose it produces a similar time course of blood levels as a single I.V. dose of 4 mg/kg. Blood levels after multi-dose treatment were not determined. The results of this study showed dose-related parental ataxia without evidence of adverse effects on male or female fertility or general reproduction performance. The segment II or teratology studies were conducted in rats and rabbits administered the midazolam maleate formulation intravenously. The high dose in rats and rabbits was 4 mg/kg/day and 2 mg/kg/day, respectively. These dosages produced slight to moderate maternal ataxia and sedation without evidence of drug-related teratogenesis. A segment III perinatal and postnatal study in rats employed the midazolam maleate formulation administered intravenously at doses up to 4 mg/kg/day. Dose-related pharmacological signs were observed in female rats without evidence of adverse effects on the offspring.

Two year carcinogenicity studies were performed in B6C3F1 mice and Charles River Sprague Dawley rats with dietary doses of midazolam maleate up to 80 mg/kg/day. Preliminary reports of these studies have been submitted and contain complete histopathological evaluations of the liver. Data regarding all of the other organs under study have not been received. Recently, however, we received a statement about thyroid histopathology which indicated a two-fold increase in follicular tumors in male rats treated at the high dose (Submission April 20, 1984). An evaluation of this will be deferred until we receive the final reports of the carcinogenicity studies in mice and rats which are expected within a few months. In the meantime the following data appear relevant.

An increased incidence of primary liver tumors, adenomas and carcinomas, was observed in high dose female mice. The increase was statistically significant, by 18 months (47% versus 5% in control female mice) and between 18 months to 2 years (79% versus 8% in controls). The increased incidence in midazolam treated females is much greater than reported for the laboratory control (3-4%) and in the literature for spontaneously occurring tumors in female B6C3F1 mice (0-21%); JNCI 62: 957, 1979 and JNCI 66: 1175, 1981). The incidence of liver tumors in male mice treated with the high dose of midazolam (45%) is not remarkably different from the incidence in the concurrent male controls (38%) and it is within the range for spontaneous tumors in males of this strain (7-58%; JNCI 66: 1175, 1981). Primary liver tumors were not increased in male or female rats treated for 2 years with the same doses of midazolam on an mg/kg basis.

The sponsor suggests that the liver tumors in female mice were secondary to liver cell hypertrophy which was induced by long term treatment with high doses of midazolam. They cite the experience with phenobarbital as an example of a liver enzyme inducer and an agent that causes liver hypertrophy and tumors in male and female CFI mice. (IARC monograph 13, 1977). The overall incidence of liver hypertrophy in high dose male mice was 71% (tumors incidence of 45%) while the incidence of hypertrophy for high dose female mice was 49% (tumor incidence of 73%). A greater number of high dose male mice died before 24 months which may account for the seemingly lack of correlation between tumors and hypertrophy. A more complete evaluation of the final report when it is received may shed light on this issue. Among currently marketed benzodiazepine drugs, there is evidence from a single study that oxazepam at high dietary doses induces a high incidence (75%) of liver tumors in male and female Swiss Webster mice (Res. Comm. Path. Pharm. 8: 481-488, 1974). Overall comparisons, with respect to animal liver tumors are not possible for all members of this class because while some drugs do not increase the incidence of tumors in rats and mice, several other drugs have rat but not mouse carcinogenicity studies, and a few of the drugs do not have adequate studies in either rats or mice (Pharmacology reviews 5/13/80 and 12/81; NDA 13-263). All new drugs of this class are expected to have rat and mouse carcinogenicity studies and oxazepam and chlordiazepoxide have ongoing rat carcinogenicity studies. For midazolam, mutagenicity tests in *Salmonella typhimurium* (TA 1535, 1537, 1538, 98, and 100), Chinese hamster lung cells (V79), human lymphocytes, and the micronucleus assay in mice did not show evidence of mutagenic activity. The lack of effect in mutagenicity tests and the fact that only female mice treated with high doses of midazolam developed tumors lends support to the idea of an initial epigenetic mechanism (e.g., sex hormone imbalances; Cancer Res. 36: 2584-2588, 1976) as opposed to a mechanism involving genetic mutations. Tumors that result from an obligatory initial epigenetic mechanism may be more likely associated with treatment of high drug dosages for long periods of time. These conditions do not apply to the proposed uses of the parenteral form of midazolam.

Recommendations:

1 The preclinical pharmacological and toxicological properties of the parenteral form of midazolam have been sufficiently characterized to support its approval for the proposed indications.

2 Labeling:**Carcinogenesis, mutagenesis, impairment of fertility**

Two year oral carcinogenicity studies in mice and rats with midazolam maleate at dosages up to 80 mg/kg/day have been conducted and analysis of the data is in progress. Histopathological evaluation of the liver tissue has been completed and shows an increased incidence of liver adenomas and carcinomas in female mice receiving the highest dosage level. The incidence of liver tumors in male mice was not remarkably different from the incidence in the concurrent controls or in the historical control for this strain of mouse. Liver tumors were not increased after midazolam treatment in male or female rats.

Midazolam did not have mutagenic activity in *Salmonella typhimurium* (5 bacterial strains), Chinese hamster lung cells (V79), human lymphocytes, or in the micronucleus test in mice.

A reproduction study in male and female rats did not show impairment of fertility.

Pregnancy: Teratogenic effects: Pregnancy Category D. See "Warnings" section.

Usage in Pregnancy:

Midazolam may cause fetal harm when administered to a pregnant woman. An increased risk of congenital malformations associated with the use of diazepam and chlordiazepoxide have been suggested in several studies. Teratology studies with midazolam in rats and rabbits at I.V. doses up to about 10X the human dose of 0.35 mg/kg did not induce malformations. Nevertheless, because of the human data with other benzodiazepines, if midazolam is used in pregnancy or the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Nonteratogenic effects:

Midazolam has not been evaluated in obstetrics. Transplacental distribution of other benzodiazepines, however, has occurred during the last weeks of pregnancy and has resulted in neonatal CNS depression. In animal studies, midazolam crosses the placenta in both rats and sheep although studies in rats have not indicated any adverse fetal or neonatal effects.

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CC:
NDA 18-654
HFN 120
HFN-120/JContrera init. 4/12/84
HFN-120/AWilk
HFN-180
rd/rbe/5/1/84/5/14/84
ft//5/21/84
document #0548C

NDA 18-654

Versed (midazolam) Injectable

29 1986

Pharmacology and Toxicology Review
Amendment 11/27/85

Subject: Labeling Revision

Recommendation:

Carcinogenesis: (Refer to FDA letter, page 7)

Midazolam maleate was administered with diet in mice and rats for two years at dosages of 1, 9, and 80 mg/kg. In female mice in the highest dose group there was a marked increase in the incidence of hepatic tumors. In high dose male rats there was a small but statistically significant increase in benign thyroid follicular cell tumors. Dosages of 9 mg/kg (25 times a human dose of 0.35 mg/kg) did not increase the incidence of tumors. The pathogenesis for induction of the liver and thyroid tumors is not known. These tumors were found after chronic administration, whereas human use will ordinarily be of single or several doses.

Comment: The dose range between the mid-dose of 9 mg/kg (no effect level) and 80 mg/kg is quite large which hinders a reasonable determination of the slope of the dose response curve. Thus, there is uncertainty as to the minimum effect dose for induction of tumors. The revised text, by stating the doses used in the studies and by giving the no effect dose, more accurately presents the findings of the carcinogenicity studies.

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cc:
Orig: NDA 18-654
HFN-120
HFN-160/D. Scally
HFN-120/J Contrera/Init/12/6/85
HFN-120/Wilk/12/6/85
ft/ml 12/10/85
DOC 0288f

NDA

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REV

N-18654-2

120 CCI
APR 15

NDA 18-654

Date Completed: April 11, 1984
Date Assigned: January 19, 1984
Date of Submission: December 15, 1982
Date Received: December 15, 1982

MEDICAL OFFICER'S REVIEW

Name of Sponsor: Hoffman-LaRoche
Nutley, New Jersey 07110

Name of Drug: Generic: Midazolam Injectable

Category (Use) of Drug: Sedative for short diagnostic or endoscopic procedures.

Dosage Form and Route of Administration: Solution of midazolam hydrochloride 5 mg/ml in ampuls for parenteral injection.

Type of Submission: Original New Drug Application submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.1.

General Comments:

This review encompasses only a portion of the clinical submission comprised of 30 studies of midazolam as an intravenous sedative in patients undergoing diagnostic endoscopic or cardiovascular procedures. The endoscopic procedures included bronchoscopy, gastroscopy and cystoscopy. The cardiovascular procedures included cardiac catheterization, angiography and cardioversion. Studies were conducted with or without meperidine premedication and specific types of studies were conducted within a multicenter format and were pooled for analysis. The type of studies and their multicenter organization were as follows:

Table 1
STUDY ORGANIZATION

<u>Investigator</u>	<u>Study number</u>
<u>Protocol 2234A - Bronchoscopy Without Meperidine Premedication</u>	
Steinberg, H.	106
Robertson, J. K.	108
Ahmad, H.	112
Kvale, P.A.	121
<u>Protocol 2235A - Bronchoscopy With Meperidine Premedication</u>	
Khan, F. A.	107
Balchum, O. J.	117
Jenkinson, S. J.	118
Mariencheck, W. I.	123

Protocol 2236A - Cystoscopy Without Meperidine Premedication

Lawson, R. K.	105
Evans, A. T.	113
Wein, A. J.	119
Chasapakis, G.	150

Protocol 2237A - Cystoscopy With Meperidine Premedication (Females)

Witherington, R.	116
Witherington, R.	126

Protocol 2237B - Cystoscopy With Meperidine Premedication (Males)

Fair, W. R.	124
Corsen, G.	125
Hanno, P. M.	127
Lawson, R. K.	128

Protocol 2238A - Gastroscopy Without Meperidine Premedication

Lanza, F. L.	101
Dunn, D. G.	110
Isenberg, J. I.	120

Protocol 2239A - Gastroscopy With Meperidine Premedication

White, P. F.	102
Morrissey, J. F.	104

Protocol 2241A - Cardioversion Without Meperidine Premedication

Lee, T.	109

Protocol 2242A - Cardiac Catheterization With Meperidine Premedication

Gensini, G.	114
Hendrix, G.	115
Ludbrook, P. A.	122

Protocol 1032 - Cardiac Catheterization Without Meperidine Premedication
(Hemodynamic Study)

Fragen, R.	007

Protocol 2243A - Angiography Without Meperidine Premedication

Ludbrook, P. A.	103
Ryan, T. J.	111

Pooled Study Summary

Study Nos. 106, 108, 112, 121, Protocol 2234A

Title: A comparison of Midazolam and Diazepam Administered Intravenously with Local Anesthesia for Bronchoscopy.

Subjects

Eighty three patients (ASA I-II) undergoing diagnostic bronchoscopy for the first time participated in the study. The study population consisted of 30 non-pregnant females and 53 males ranging in age from 20 to 85 years. In the midazolam group there were 28 males and 14 females with a mean age of 54.8 years (range 21-85). In the diazepam group there were 25 males and 16 females with a mean age of 55.9 years (range 20-85).

ResultsDifferences Among Study Centers

Efficacy data from the four patients in study #112 were not included in the efficacy analysis due to limited patient enrollment.

There was a major difference between study centers in the physicians' assessments of sedation. Several of the investigators experienced difficulties with the procedure since premedication with meperidine was not allowed. Dr. Shmad (Study #112) discontinued his study because of excessive coughing and gagging of his patients. Dr. Robertson (Study #108) experienced similar problems; however, these experiences were more pronounced in the midazolam group. Dr. Steinberg (Study 105) did not have these problems; however, he had to administer maintenance sedation doses of the test drugs to almost all of his patients (77%).

Deviations From Protocol

These are addressed in the individual study summaries.

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean initial doses of 0.110 mg/kg of midazolam and 0.166 mg/kg of diazepam. Forty two percent of the patients in the midazolam group and 48% of the diazepam group required maintenance sedation doses to complete the procedure. Most of these patients were from Dr. Steinberg's study. The mean total drug doses administered were 0.146 mg/kg of midazolam and 0.210 mg/kg of diazepam.

The meantime to reach the sedative end point was significantly shorter for the midazolam group (3 minutes vs. 5.8 minutes). The average duration of the bronchoscopies was similar between treatment groups.

Physician's Assessment

Diazepam patients were significantly more cooperative and had better muscle relaxation. One center (#103) contributed most to weighing the data against midazolam.

Patient's Assessment

One hour after the procedure, sedation was rated significantly better by the midazolam group; however, this difference did not remain significant by the following day. Most patients in both groups had little or no pain associated with the bronchoscopy and were willing to undergo a future procedure the same way.

Trieger Test

There were increases in the number of dots missed and deviation from the dots in both treatment groups one hour after the bronchoscopy, with the midazolam patients displaying a statistically significant increase in deviation from the dots. By two hours these values demonstrated a downward trend, although they were still elevated.

Follow-Up Questionnaire for Amnesia

There was a small percentage of patients in each group with diminished recall of events prior to test drug administration. Following test administration both groups had diminished recall of scope introduction and withdrawal; however, midazolam patients had significantly less recall of the introduction of the bronchoscope. Significantly more patients in the midazolam group had diminished recall of the post-treatment Trieger Tests.

SafetyTable 1Clinical Adverse Experiences

<u>Possibly and Probably Related Drug Effects</u>	<u>Midazolam</u>		<u>Diazepam</u>	
	<u># Pts.</u>	<u>Percent</u>	<u># Pts.</u>	<u>Percent</u>
<u>Respiratory System</u>				
Respiration Rate Increase	22	52.4	18	43.9
Respiration Rate Decrease	9	21.4	12	29.3
Respiratory Depression	1	2.4	0	0
Airway Obstruction	1	2.4	0	0
Coughing	1	2.4	0	0
Bronchospasm	1	2.4	0	0
<u>Cardiovascular System</u>				
Pulse Increase	12	23.6	13	31.7
Pulse Decrease	4	9.5	4	9.8
MAP Increase	1	2.4	4	9.8
MAP Decrease	9	21.4	4	9.8
Hypotension	1	2.4	0	0
Phlebitis	0	0	2	4.9
Tenderness of Vein	0	0	2	4.9
Redness of Vein	1	2.4	1	2.4
Induration of Vein	0	0	1	2.4
<u>Central Nervous</u>				
Headache	0	0	1	2.4
<u>Gastrointestinal</u>				
Vomiting	1	2.4	1	2.4
<u>Miscellaneous</u>				
Agitated	0	0	1	2.4
<u>Remotely Related Effects</u>				
Bradycardia	1	2.4	0	0
Blood loss	1	2.4	0	0

No changes in vital signs were observed during induction of sedation.

Summary and Conclusions

In this multicenter study the results of four randomized, double-blind parallel group studies included 83 patients undergoing diagnostic bronchoscopy for the first time, using atropine premedication and a topical anesthetic agent. Significantly less time was required by the midazolam-treated patients to reach the sedative end point. Forty two and forty eight percent of patients in the midazolam and diazepam groups respectively required maintenance sedation doses.

On the physician's assessment, significantly better muscle relaxation and cooperation were ascribed to the diazepam group. This protocol did not allow premedication with meperidine and several investigators experienced difficulty in performing the bronchoscopy because of excessive patient coughing and gagging.

On the one-hour patient questionnaire, midazolam-treated patients assessed quality of sedation as significantly better. There were no significant differences between group in willingness to undergo a future procedure the same way and for degree of pain associated with the bronchoscopy.

With respect to psychomotor recovery, midazolam patients has significantly more impairment one hour following the bronchoscopy.

Most patients could recall events prior to the test drug administration. Significantly more midazolam patients could not recall the bronchoscopy and the post treatment Triger Tests.

Most changes in vital signs were not clinically significant. One patient experienced hypotension and respiratory depression following the administration of midazolam. No corrective measures were required and the procedure was successfully completed. Another patient who received midazolam had too much muscle relaxation which caused brief occlusion of the airway by the tongue. One patient experienced severe agitation following the administration of diazepam forcing the investigator to cancel the procedure.

Two diazepam and one midazolam-treated patients had evidence of venous irritation at the intravenous injection site at the follow-up examination.

In this study midazolam was shown to be as safe and effective as diazepam in inducing sedation for bronchoscopy. The physicians did not rate midazolam as effective as diazepam for some parameters, but the patients experienced better sedation and had less recall of the procedure. Several physicians had difficulty in completing the bronchoscopy because of excessive coughing and gagging of the patients, and a relatively large percentage of patients required maintenance doses. These conditions may have occurred because of the elimination of a narcotic premedicant.

Study No. 106

Title: A Comparison of Midazolam and Diazepam Administered Intravenously With Local Anesthesia for Bronchoscopy

Investigator: The objective of this study was to compare the sedative and amnestic properties administered during local anesthesia for bronchoscopy.

Experimental Design

Randomized, double-blind study in 40 patients undergoing bronchoscopy for the first time. The design of this study was similar to that of study 121 since this was a multicenter study following the same protocol.

Subjects

There were 18 non-pregnant females and 22 males ranging in age from 25 to 85 years (ASA I-II). In the midazolam group there were 11 males and a females with a mean age of 58.8 years (range 25-82). In the diazepam group there were 11 males and 9 females with a mean age of 60.8 years (range 26-85).

Study Drugs: See Study 121.

ResultsDeviations from Protocol

Patient (diazepam, 0.429 mg/kg) was excluded from efficacy analyses for receiving an excludable concomitant medication (Percodan) within twenty four hours of the procedure.

Three patients omitted answering a question on the 24 hour questionnaire:

Patient	(Midazolam) - rual injection in thigh
Patient	(Diazepam) - Future procedure done same way
Patient	(Diazepam) - Recall scope introduction

Most patients did not have vital sign measurements taken after the bronchoscopy; therefore, only a few patients' data were analyzed for changes in vital signs during the recovery period.

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.094 mg/kg of midazolam and 0.131 mg/kg of diazepam. Seventy percent of the midazolam group and 84 percent of the diazepam group required maintenance sedation doses to complete the procedure. Midazolam-treated patients required a mean total drug dose of 0.158 mg/kg, while diazepam-treated patients required 0.236 mg/kg. There was no significant difference between groups with respect to time to reach the sedative endpoint.

Physician's Assessment

The physician's assessment of sedation was in most instances "good" to "excellent" for both midazolam and diazepam treatment groups. There were no significant differences between treatments in the physician's assessment of sedation.

Patient's Assessment

Midazolam patients rated quality of sedation significantly better one hour after bronchoscopy; however, there was no significant difference between treatments in the following day. Midazolam - treated patients reported significantly less pain associated with the bronchoscopy. Most patients were willing to undergo the procedure the same way again.

Trieger Test

Midazolam-treated patients missed significantly more dots one hour after the procedure, toward the baseline values.

Follow-Up Questionnaire for Amnesia

One hour after the procedure, both treatment groups had diminished recall of the bronchoscopy; however, midazolam - treated patients had significantly less recall of the procedure. Diminished recall was extended to two hours in several patients in both treatment groups with respect to failure to recall the post-treatment Trieger Tests.

Safety

Patient (diazepam) had evidence of phlebitis (erythema and induration) for three days following the study. Tenderness of the intravenous injection site was also present for nine days following the study. This patient also had a headache following the procedure. Patient (midazolam) experienced bradycardia; however, this was considered to be remotely related to the test drug treatment.

Table 1

Clinical Adverse Experiences

<u>Possibly and Probably Related Drug Expects</u>	<u>Number of Patients</u>	
	<u>Midazolam</u>	<u>Diazepam</u>
<u>Respiratory System</u>		
Respiration Rate Increase	5	5
Respiration Rate Decrease	2	1
<u>Cardiovascular System</u>		
Pulse-Increase	1	2
Pulse-Decrease	1	0
MAP - Increase	0	2
MAP - Decrease	0	1
Pnebitis	0	1
Tenderness of Vein	0	1
<u>Central Nervous</u>		
Headache	0	1
<u>Remotely Related Drug Effect</u>		
<u>Cardiovascular</u>		
Bradycardia	1	0

Most changes in vital signs were transient and were most often associated with the bronchoscopy. No changes in vital signs were observed during induction of sedation.

Summary and Conclusions

This randomized, double-blind study compared the use of midazolam with diazepam to provide sedation during bronchoscopy. As adjuncts to local anesthetic agents, both drugs were effective intravenous sedative agents for bronchoscopy. Ratings of sedation by the physician were in most instances "good" to "excellent" for both test medications. One hour after the bronchoscopy, midazolam patients evaluated quality of sedation significantly better and reported significantly less pain associated with the procedure than did diazepam-treated patients.

One hour after the procedure, both treatment groups had diminished recall of the bronchoscopy; however, the midazolam group had significantly less recall of the procedure. Midazolam-treated patients had significantly less recall of the introduction of the bronchoscopy, although most patients had diminished recall of the introduction and withdrawal of the bronchoscope. Several patients in both treatment groups had diminished recall for the post-treatment

Trieger Tests extending to two hours. Midazolam patients missed significantly more tests on the one hour Trieger Test, but at two hours the results had returned to near the baseline value.

Transient fluctuations in vital signs were observed in both treatment groups but were not considered clinically significant. One diazepam-treated patient had evidence of phlebitis. One midazolam-treated patient had bradycardia, but this was considered to be remotely related to the test drug.

This study showed that midazolam, when used in combination with a local anesthetic agent, is as safe and effective as diazepam in inducing sedation for bronchoscopy. It was also effective in inducing diminished recall of the procedure.

Study No. 108

Title: A Comparison of Midazolam and Diazepam Administered Intravenously with Local Anesthesia for Bronchoscopy.

Investigator: K. Joy Robertson, M.D.

Objective: The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam when administered during local anesthesia for bronchoscopy.

Experimental Design

Randomized, double-blind study in the patients undergoing bronchoscopy for the first time. The design of this study was similar to that of Study 121 since this was a multicenter study following the same protocol.

Subjects

There were 3 non-pregnant females and 13 males ranging in age from 20 to 80 years (ASA I-II). In the midazolam group there were 7 males and 1 female with a mean age of 36.5 years (range 21-69). In the diazepam group there were 6 males and 2 females with a mean age of 41.3 years (range 20-80).

Study Drugs: See Study 121

ResultsDeviations from Protocol

Patient who received 0.250 mg/kg of diazepam, developed severe agitation which required termination of the bronchoscopy. This patient's data were excluded from all efficacy tables.

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.119 mg/kg of midazolam and 0.224 mg/kg of diazepam. One midazolam and two diazepam patients required additional doses to maintain sedation. Midazolam-treated patients required a shorter mean time to sedation of 2.45 minutes compared with 4.75 minutes for diazepam-treated patients.

Physician's Assessment

There were no significant differences between treatment groups. Control of laryngospasm "excellent" in both treatment groups.

Patient's Assessment of Sedation

On both rating occasions, most patients in both treatment groups reported the quality of sedation as "good" or "excellent". All patients described little or no pain associated with the bronchoscopy. Most patients said that they would elect to undergo the procedure the same way again.

Trieger Test

Patients in both treatment groups had an increase in number of dots missed and total deviation from the dots compared with baseline values at one hour following the bronchoscopy. At two hours these values were returning toward baseline for midazolam patients while diazepam patients had an increase in these values compared with their one hour results.

Follow-Up Questionnaire for Amnesia

Several patients in each group had no recall of spraying of the throat. Failure of recall of bronchoscope introduction and withdrawal was experienced by most patients in both treatment groups. Several patients had prolonged failure of recall since on the following day they could not recall the post-treatment Trieger Tests.

Safety

Patient _____ developed severe agitation after receiving 0.250 mg/kg of diazepam which caused the investigator to cancel the bronchoscopy. One midazolam-treated patient _____ developed vomiting and coughing.

Table 1

Clinical Adverse Experiences

<u>Possibly and Probably Related Drug Effects</u>	<u>Number of patients</u>	
	<u>Midazolam</u>	<u>Diazepam</u>
<u>Respiratory System</u>		
Respiratory Rate Increase	7	5
Respiratory Rate Decrease	2	4
Coughing	1	0
<u>Cardiovascular System</u>		
Pulse Increase	6	4
Pulse Decrease	1	0
MAP Increase	1	1
MAP Decrease	2	1
<u>Gastrointestinal</u>		
Vomiting	1	0
<u>Miscellaneous</u>		
Agitated	0	1

No changes in vital signs were observed during induction of intravenous sedation. Most changes were transient and were most often associated with the bronchoscopy. A severe increase in mean arterial pressure was observed in one midazolam patient both during bronchoscopy and recovery. Severe increases in pulse rate and respiration rate both during bronchoscopy and recovery were observed in several patients in both treatment groups. One diazepam patient also had a severe decrease in respiration rate during recovery.

Summary and Conclusions

This study was still in progress at the time of submission and a statistical analysis of the results was not undertaken due to the limited number of patients studied.

One patient developed severe agitation after receiving diazepam, which forced the investigator to cancel the bronchoscopy. One midazolam - treated patient experienced vomiting and coughing. Transient fluctuations in blood pressure, pulse and respiration rate were noted but were not considered clinically significant. No patient in either treatment group had evidence of venous irritation following the study.

Study No. 112

Title: A Comparison of Midazolam and Diazepam Administered Intravenously with Local Anesthesia for Bronchoscopy.

Investigator: Muzaffar Shmad, M.D.

Objective: The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam when administered during local anesthesia for bronchoscopy.

Experimental Design

Randomized, double-blind study in 4 patients undergoing bronchoscopy for the first time. The design of this study was similar to that of Study 121 since this was a multicenter study following the same protocol.

Subjects

There were four males ranging in age from 53 to 60 years (ASA I-II). In the midazolam group there were 3 patients, 53 to 55 years of age in the diazepam group there was one patient, 60 years of age.

Study Drugs: See Study 121.

Results

This study was prematurely discontinued after entry of 4 patients due to difficulty encountered by the investigator in performing the bronchoscopy without using a narcotic cough suppressant (investigator's routine procedure) as a premedication. The investigator rated both drugs poor in controlling the cough reflex.

Safety

A 54 year old patient with a history of arteriosclerotic heart disease, experienced hypotension and respiratory depression following administration of 0.181 mg/kg of midazolam. No corrective measures were required, and the bronchoscopy was successfully completed. This patient also experienced coughing during the procedure. For three days following the study, redness of the vein was also observed.

Patient 1 (midazolam) experienced too much muscle relaxation which caused brief occlusion of the airway by the tongue. This patient also experienced coughing during the bronchoscopy.

Table 1Clinical Adverse Experiences

<u>Possibly and Probably Related Drug Effects</u>	<u>Number of Patients</u>	
	<u>Midazolam</u>	<u>Diazepam</u>
<u>Respiratory System</u>		
Respiration Rate Increase	3	1
Respiration Rate Decrease	3	1
Respiratory Depression	1	0
Airway obstruction	1	0
<u>Cardiovascular system</u>		
Pulse Increase	2	1
Pulse Decrease	0	1
MAP Decrease	2	1
Hypotension	1	0
Redness of Vein	1	0

No changes in vital signs were observed during the induction of sedation. Midazolam-treated patients had severe increases or decreases in respiration rate. One midazolam patient also had a severe increase in pulse rate.

Summary

A statistical analysis of this study was not possible due to the limited number of patients studied. Changes in vital signs were observed in all patients both during the bronchoscopy and recovery. One midazolam-treated patient experienced respiratory depression and hypotension during the procedure, however, no corrective treatment was necessary. Another patient who received midazolam had excessive muscle relaxation of the tongue which caused brief occlusion of the airway. These two patients also experienced coughing during the procedure. One midazolam-treated patient experienced redness at the intravenous injection site for three days following the procedure.

Study No. 121

Title: A comparison of Midazolam and Diazepam Administered Intravenously with Local Anesthesia for Bronchoscopy.

Investigator: Paul A. Kvale, M.D.

Objective: The objective of this study was to compare sedative and amnestic properties of intravenous midazolam and diazepam when administered during local anesthesia for bronchoscopy.

Experimental Design

This study was in progress at the time of submission; therefore, this report contains an analysis of the results in the first 23 patients. This is a randomized, double-blind, parallel-group study.

Prior to bronchoscopy midazolam or diazepam was administered by random coded assignment. Immediately following the bronchoscopy the physician, who was unaware as to which test medication had been administered evaluated as excellent, good, fair or poor the sedative effects produced by the test medication. These assessments included: (1) patient cooperation, (2) muscle relaxation, (3) ease of bronchoscopic examination, (4) control of gag reflex, (5) control of laryngospasm, (6) control of bronchospasm, (7) control of cough reflex, (8) control of retching and vomiting, (9) control of salivation, and (10) overall tolerance of the procedure. One hour after bronchoscopy and one day later in a follow-up questionnaire, patients evaluated the sedation during the procedure as excellent, good, fair or poor. Additionally, on both occasions, patients were asked whether they would elect to undergo a future bronchoscopy the same way, if necessary. One hour after bronchoscopy patients evaluated the bronchoscopic procedure as not painful, somewhat painful or very painful and whether they could recall none, some or all of the bronchoscopy. In the follow-up questionnaire, patients were also asked whether they could recall clearly, vaguely or not at all events before, during and after bronchoscopy.

Recovery from sedation was assessed by the Trieger Test which was completed by the patient before medication (baseline) and at 60 and 120 minutes following the completion of the bronchoscopy. Each Trieger Test was evaluated for the number of dots missed and the total deviation (mm) from the dots.

Blood pressure, respiratory rate and pulse rate were monitored before, during and after bronchoscopy. Changes in vital signs greater than 20% from baseline were identified as possible adverse experiences. The severity of these changes were categorized as:

- mild - a change $\geq$ 20 percent but $<$ 30 percent from baseline
- moderate - a change $\geq$ 30 percent but $<$ 50 percent from baseline
- severe - a change $\geq$ 50 percent from baseline or treatment required.

Clinical adverse experiences were further categorized according to the phase of the study. The phases of the study were defined as follows:

induction = period of test drug administration
maintenance = period of bronchoscopy
recovery = post bronchoscopy until discharge

Seven to 14 days following the procedure the intravenous injection site was examined for tenderness, redness and induration.

Subjects

There were 9 non-pregnant females and 14 males ranging in age from 23-85 years. In the midazolam group there were 7 males and 4 females with a mean age of 61.2 years (range 34-85). In the diazepam group there were 7 males and 5 females with a mean age of 57.1 years (range 23-84).

Study Drugs

Thirty minutes before bronchoscopy atropine 0.5 - 0.6 mg was administered intramuscularly. Following topical anesthetic administration, 10-15 mg of either midazolam or diazepam was administered intravenously over a 2-3 minute period. Elderly patients (as identified by the investigator) received 5.0-7.5 mg of the test medications over the same time interval. Incremental doses (25% of initial dose) were administered, if necessary, until the patient's speech became thickened and slurred but the patient was still responsive to verbal commands. When needed, additional doses were administered to maintain sedation.

Results

Deviation from Protocol

Midazolam patient _____ (0.078 mg/kg) was terminated from the study due to pharyngeal bleeding and bronchospasm resulting from a pre-existing condition. Diazepam patient _____ did not receive the total injected dose (3 ml) intravenously since the IV infiltrated during injection. They were excluded from efficacy analysis but their data was included in all safety analyses.

The Trieger Test results of midazolam patient _____ were not included in the efficacy analysis since the patient was uncooperative in completing the Trieger Tests. This patient did not complete the 24 hour questionnaire. The responses to recall of the Trieger Test by midazolam patient _____ were not included in the analysis because the patient recalled only one test but did not know which one it was.

Three patients did not answer several questions on the one or 24 hour questionnaires:

Patient (midazolam) - One hour questionnaire:
Future procedure same way

Patient (diazepam) - 24 hour questionnaire: 40
Future procedure same way

Patient (midazolam) - 24 hour questionnaire:
Recall of scope withdrawal

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.118 mg/kg of midazolam and 0.144 mg/kg of diazepam. Patient required an additional 10.038 mg/kg of midazolam to maintain sedation. The average time to reach the sedative end point was significantly shorter for midazolam than for diazepam, the former time being less than half that of the latter drug. The duration of bronchoscopy was similar for both groups.

Physician's Assessment

Assessments of sedation were in most instances "good" to "excellent" for both groups. Control of cough reflex was rated "fair" to "good" in both groups. There were no significant intergroup differences.

Patient's Assessment

One hour after the procedure, quality of sedation was rated significantly better by midazolam-treated patients, although on the following day this difference was not present. Most patients reported little or no pain associated with the bronchoscopy and indicated they would elect to undergo a future procedure the same way again.

Trieger Test

There were no statistically significant differences between the two groups in recovery from sedation. There was an increase in number of dots missed and total deviation from the dots compared with the baseline in both groups one hour after bronchoscopy. By two hours the results returned toward baseline values.

Follow-Up Questionnaire for Amnesia

There were no significant differences between treatment groups on any of the recall questions. All but one midazolam patient could recall introduction and withdrawal of the bronchoscope, while more than half of the diazepam patients could recall either the introduction or withdrawal of the bronchoscope. Failure to recall the post-treatment Trieger Tests was more pronounced for the one hour test (4/9) than for the two hour test (6/9).

Safety

Patient _____ (midazolam) had pharyngeal bleeding during the procedure which aggravated a pre-existing cough and caused the patient to have bronchospasm. The bleeding was controlled by intubation and Adrenalin. Bronchospasm was controlled with Demerol, Adrenalin, Xylocaine, Medrol and Vaponefrin.

Patient _____ (diazepam) developed phlebitis at the intravenous injection site. Tenderness, redness and induration were observed for 10 days following the study.

Table 1Clinical Adverse Experiences

<u>Possibly and Probably Related Drug Effects</u>	<u>No. Pts.</u>	
	<u>Midazolam</u>	<u>Diazepam</u>
<u>Respiratory System</u>		
Respiration Rate Increase	7	6
Respiration Rate Decrease	2	6
Bronchospasm	1	0
<u>Cardiovascular System</u>		
Pulse Increase	3	6
Pulse Decrease	2	3
MAP Increase	0	1
MAP Decrease	5	1
Tenderness of Vein	0	1
Redness of Vein	0	1
Induration of Vein	0	1
<u>Integumentary</u>		
Phlebitis at Site of Injection	0	1
<u>Remotely Related Drug Effect</u>		
<u>Hemic-Lymphatic</u>	1	0

No changes in vital signs were observed during induction of intravenous sedation. Most changes in vital signs were transient and were most often associated with the bronchoscopy. Most changes were mild or moderate with very few classified as severe. Severe increases in respiration rate were observed in both treatment groups during both the bronchoscopy and during the recovery period. One diazepam - treated patient had a severe decrease in respiration rate during the recovery period.

Summary and Conclusions

This randomized, double-blind study compared the use of midazolam with diazepam to provide sedation during bronchoscopy. The study was still in progress at the time of submission and this report represents the results in 23 patients. As adjuncts to local anesthetic agents, both drugs were effective intravenous sedative agents for bronchoscopy. Ratings of sedation by the physician were "good" to "excellent" for both test medications except for control of cough reflex which was rated "fair" to good. Quality of sedation was rated significantly better by the midazolam patients one hour later; however, this difference was not present on the following day. Most patients in both treatment groups reported little or no pain associated with the bronchoscopy and indicated that they would elect to undergo the procedure the same way again.

Recovery from sedation was comparable between treatments. Both groups showed some impairment of performance one hour following bronchoscopy. Failure to recall the bronchoscopy was induced in all but one midazolam patient, but more than half of the diazepam patients had recall of the procedure. Failure of recall was extended in some midazolam patients for two hours.

One midazolam - treated patient developed pharyngeal bleeding during the procedure which aggravated a pre-existing cough and caused the patient to have bronchospasm. This was treated and relieved. One diazepam - treated patient had evidence of phlebitis at the intravenous injection site for 10 days following the study. Transient fluctuations in vital signs were noted in both treatment groups but were not considered clinically significant.

This study showed that midazolam, in combination with local anesthetic, was safely used to induce sedation during bronchoscopy. Midazolam was as effective as diazepam in providing patient sedation, and was superior in inducing failure of recall for the procedure.

Pooled Study Summary

Study Nos. 107, 117, 118, 123, Protocol 2235A

Title: A Comparison of Midazolam and Diazepam in Combination With Meperidine During Local Anesthesia for Bronchoscopy

Subjects

Eighty eight patients (ASA I, or II) undergoing diagnostic bronchoscopy for the first time participated in the study. The study population consisted of 36 non-pregnant females and 52 males ranging in age from 20 to 79 years. In the midazolam group there were 43 patients comprised of 22 males and 21 females with a mean age of 49.8 years (range 25-72). In the diazepam group there were 45 patients comprised of 30 males and 15 females with a mean age of 53/2 years (range 20-79).

Results

Differences Between Study Centers

An additional dose of test medication to maintain sedation was administered to six midazolam and five diazepam patients in Dr. Balchum's study (#117). None of the patients in the other studies required maintenance sedation doses. The need for maintenance sedation doses in this study was related to the longer time required for completion of the bronchoscopy. In the other three studies, the average length of the procedure was 25 minutes compared with 51 minutes in Dr. Balchum's study.

Deviations from Protocol

These are addressed in the individual study reports.

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean initial doses of 0.094 mg/kg of midazolam and 0.104 mg/kg of diazepam. An additional dose to maintain sedation was required by six (6 of 9) midazolam and five (5 of 10) diazepam patients in Dr. Balchum's study (#117). The reason for this has already been detailed in the beginning of this section. The mean time to reach the sedative end point of slurred speech was 4.4 minutes for both groups of patients.

Physician's Assessment of Sedation

A 4-point scale (excellent, good, fair, poor) was used by the physician to assess the sedative effects of the test medications. There were no significant differences between treatment groups in the assessment. Most parameters were assessed as "good" or "excellent" by the physician. Control of cough reflex, however, was only rated "fair" to "good" for both test drugs.

Patient's Assessment of Sedation

On two occasions, one hour after the procedure and on the following day, patients assessed the sedative effects of the test drugs. One hour after the procedure, there was no significant difference between treatment groups. On the following day, however, midazolam-treated patients rated sedation significantly better. The majority of midazolam patients (97%) and all of the diazepam patients reported little or no pain associated with the procedure. Most patients were willing to have a future bronchoscopy done the same way.

Trieger Test

There were no statistically significant differences between treatment groups in psychomotor recovery from sedation. There were increases in number of dots missed and deviation from the dots in both treatment groups one hour after bronchoscopy. At two hours the results in both treatment groups had returned to near the baseline values. While the midazolam group approached closer to the baseline values, the difference was not statistically significant.

Follow-Up Questionnaire for Amnesia

Most patients in both groups could recall events performed before test drug administration. A statistically significantly greater number of midazolam patients had diminished recall of the baseline Trieger Test. Following test drug administration, both test groups had diminished recall of the bronchoscopy. Midazolam-treated patients had significantly less recall of scope introduction. The majority of patients recalled the one and two hour Trieger Tests.

Safety

Three patients who received midazolam experienced adverse reactions which forced cancellation of the bronchoscopy. These adverse experiences were all felt to be related to the combined effects of midazolam/meperidine.

<u>Study</u>	<u>Patient number</u>	<u>Adverse Reactions</u>
117		hypotension and apnea
107		deep sedation and apnea
107		deep sedation and hypotension

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Table 1
Clinical Adverse Experiences

	<u>Midazolam</u>		<u>Diazepam</u>	
	<u># pts.</u>	<u>Percent</u>	<u># pts.</u>	<u>Percent</u>
Possibly and Probably Related Drug Effects				
<u>Respiratory System</u>				
Respiration Rate Increase	23	53.5	29	64.4
Respiration Rate Decrease	13	30.2	16	35.6
Apnea	2	4.7	1	2.2
<u>Cardiovascular System</u>				
Pulse Increase	18	41.9	21	46.7
Pulse Decrease	10	23.3	6	13.3
MAP Increase	6	14.0	10	22.2
MAP Decrease	11	25.6	5	11.1
Hypotension	2	4.7	1	2.2
Tenderness of Vein	0	0	1	2.2
Redness of Vein	0	0	1	2.2
Induration of Vein	1	2.3	0	0
<u>Central Nervous</u>				
Headache	1	2.3	0	0
<u>Gastrointestinal</u>				
Nausea	2	4.7	2	4.4
Vomiting	0	0	1	2.2
<u>Musculoskeletal</u>				
Hiccoughs	1	2.3	0	0
<u>Integumentary</u>				
Pain During Injection of study drug	0	0	4	8.9
<u>Miscellaneous</u>				
Chest Pain	0	0	1	2.2
Deep Sedation	2	4.7	0	0
Remotely Related Drug Effect				
Laryngitis	1	2.3	0	0
Epiglottitis	1	2.3	0	0
Laryngospasms	0	0	1	2.2
Headache	1	2.3	0	0
Clenching of Jaws	1	2.3	0	0
Blurring of Vision	1	2.3	0	0
Number of Adverse Experiences Reported	97		100	
Number of Patients with Adverse Experiences	38	88.4	41	91.1
Number of Patients Treated	43		45	

Summary and Conclusions

In this multicenter study the results from randomized, double-blind parallel group studies included 88 adults. It was demonstrated that both midazolam and diazepam were effective intravenous sedative agents for bronchoscopy when used as adjuncts to intramuscular meperidine and local anesthetic. All patients received meperidine, atropine, and a topical anesthetic agent prior to the procedure. Comparable levels of sedation (slurred speech) were attained with mean doses of 0.094 mg/kg of midazolam and 0.104 mg/kg of diazepam in a mean time of 4.4 minutes with either drug.

The physician's evaluation of the sedative properties of the test drugs were similar for both drugs. Patients' assessments were not significantly different one hour after the procedure; however, on the following day midazolam-treated patients rated sedation as significantly better. Most patients in both test groups reported little or no pain associated with the bronchoscopy and were willing to undergo a future procedure the same way.

Midazolam produced significantly greater anterograde recall impairment. One hour after the procedure, only 11% (4 of 35) of midazolam-treated patients could recall the procedure compared with 45% (19 of 42) of diazepam-treated patients.

Psychomotor recovery from sedation as assessed by the Trieger Test was comparable between treatments. Both treatment groups had impairment of psychomotor performance one hour after the procedure; however, two hours post-treatment the results in both treatment groups approached baseline values, demonstrating recovery from sedation.

There were reports of hypotension, apnea and deep sedation in both groups; however, in the midazolam-treated group three patients with these reactions had their bronchoscopies cancelled. No cancellations for these reasons occurred in the diazepam-treated group. There were reports of laryngospasm (diazepam) and epiglottitis and laryngitis (midazolam) which forced cancellation of the procedure. These events were all related to underlying patient conditions. These reactions were attributed to the combined effects of meperidine and the benzodiazepine. One patient in each test group had evidence of venous irritation at the follow-up examination.

This study demonstrated that IV midazolam, when used in combination with meperidine, atropine and a topical anesthetic agent is as safe and effective as diazepam in inducing sedation for bronchoscopy. Midazolam impaired recall of the procedure more effectively. There were several instances of adverse experiences in both treatment groups (deep sedation, hypotension or apnea). These effects occurred more frequently and were more severe in the midazolam group. These adverse effects were attributed to the combined effects of meperidine and midazolam.

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Study No. 107

Title: A Comparison of Midazolam and Diazepam In Combination With Meperidine During Local Anesthesia for Bronchoscopy

Investigator: Faroque A. Khan, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in adults undergoing bronchoscopy for the first time.

Experimental Design

Randomized, double-blind study in 22 adults undergoing bronchoscopy. The design of this study was similar to that of study 117 since this was a multicenter study following the same protocol.

Subjects

There were 8 non-pregnant females and 14 males ranging in age from 34 to 78 years. In the midazolam group there were 7 males and 5 females with a mean age of 53.3 years (range 36-63). In the diazepam group there were 7 males and 3 females with a mean age of 60.6 years (range 34-78).

Study Drugs: See Study 117.

Results

Deviations from Potocol

Four midazolam _____ and one diazepam patient _____ were excluded from all efficacy analyses.

Patients _____ and _____ were excluded due to violations of the protocol. Patient _____ did not complete the Trieger Test. For patient _____ the physician's assessment and patient questionnaires were not returned. Patient _____ and _____ experienced adverse effects (deep sedation with hypotension or coma) which required the postponement of bronchoscopy to a later date. Patient _____ experienced discomfort resulting from severe epiglottitis and laryngitis forcing the cancellation of the bronchoscopy. All patients who received test medications were included in safety analyses.

Only the baseline and one-hour Trieger Test Results were analyzed for patient _____ of the midazolam group. One of the Trieger Tests, done 10 minutes after the procedure, was discounted.

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.060 mg/kg of midazolam and 0.075 mg/kg of diazepam. The mean time to reach the sedative end point (slurred speech) was similar in both groups (midazolam: 7.77 minutes, diazepam: 6.94 minutes) for similar mean durations of bronchoscopy.

Physician's Assessment of Sedation

The physician's assessment of sedation was in most instances "fair" to "good" for both midazolam and diazepam-treated patients. There were no statistically significant differences between treatments in the physician's assessment of sedation.

Patient's Assessment of Sedation

One hour after the procedure 5/8 midazolam-treated patients rated the sedation "good" to "excellent" compared with 9/9 diazepam patients.

On the following day, 7/8 midazolam patients rated their sedation "good" to "excellent" compared with 9/9 diazepam patients, however, 5 of the former patients rated their treatment excellent compared with 2 diazepam patients. All patients reported little or no pain associated with the bronchoscopy and the majority of patients in both groups indicated that they would undergo future bronchoscopy the same way.

Trieger Test

On the one-hour Trieger Test, midazolam-treated patients had a greater number of dots missed and total deviation from the dots compared with baseline values than diazepam-treated patients, however, the differences were not statistically significant. By two hours, both treatment groups had returned toward the baseline values.

Follow-Up Questionnaire for Amnesia

There were no significant differences between treatments on any of the recall questions. Most midazolam and diazepam-treated patients could recall events prior to the test drug administration including the baseline Trieger Test, the meperidine injection and throat spraying, indicating absence of retrograde failure of recall. One hour after the procedure more midazolam than diazepam patients could not recall the bronchoscopy. Anterograde failure of recall, defined as lack of recall of events following the administration of the test drug, was observed in about half of the patients in both treatment groups. This extended for 5 of 8 midazolam patients and 8 of 8 diazepam patients to two hours with respect to failure to recall the post-treatment Trieger Tests.

Safety

Two patients who received midazolam had deep sedation requiring cancellation of the bronchoscopy. Patient , a 60-year old female with a history of atrial fibrillation and grand mal seizures, experienced deep sedation and hypotension after receiving 0.909 mg/kg of meperidine and 0.091 mg/kg of midazolam. Dopamine (60 mg) was given to reverse the hypotension. A 50 year old male patient experienced deep sedation and apnea (for 1 to 2 minutes) after receiving 0.833 mg/kg of meperidine and 0.083 mg/kg of midazolam. Narcan (0.4 mg) was administered and breathing resumed spontaneously. One diazepam-treated patient experienced mild hypotension upon completion of induction. No corrective measures were required; consequently, the bronchoscopy was successfully completed.

One midazolam patient had induration of the vein extending 2 cm proximal to the injection site for five days following the procedure. This patient also had mild blurring of vision and headache following the procedure; however, these symptoms were considered to be only remotely related to midazolam treatment by the investigator.

Changes in Vital Signs

The following tables indicate in which phase of the study the changes in vital signs occurred and the severity of the changes. Most changes were mild to moderate and were most often associated with the bronchoscopy. Patient who received diazepam, had a severe decrease in pulse rate during recovery. Three midazolam-treated patients had severe increases in respiration rates, one during bronchoscopy and two during recovery.

Table 1

Changes From Baseline For Mean Arterial Pressure

	<u>Number of Patients</u>	
	<u>Midazolam</u>	<u>Diazepam</u>
<u>Number of Patients Studied</u>	12	10
<u>During Induction of IV Sedation</u>		
Decrease (20-30%)	1	2
<u>During Bronchoscopy</u>		
Decrease (20-30%)	1	-
Decrease (30-50%)	1	-
Increase (20-30%)	1	-
<u>During Recovery</u>		
Decrease (20-30%)	4	-
Decrease (30-50%)	1	1

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Table 2

Changes From Baseline For Pulse Rate

	Number of Patients	
	Midazolam	Diazepam
<u>Number of Patients Studied</u>	12	10
<u>During Induction of IV Sedation</u>		
Decrease (20-30%)	1	-
Increase (30-50%)	-	1
<u>During Bronchoscopy</u>		
Decrease (20-30%)	1	-
Increase (20-30%)	1	3
Increase (30-50%)	2	1
<u>During Recovery</u>		
Decrease (20-30%)	1	1
Decrease (30-50%)	-	1
Decrease ($\geq$ 50%)	-	1
Increase (20-30%)	1	-
Increase (30-50%)	2	1

Table 3

Changes From Baseline For Respiration Rate

	Number of Patients	
	Midazolam	Diazepam
<u>Number of Patients Studied</u>	12	10
<u>During Induction of IV Sedation</u>		
Decrease (20-30%)	-	1
Increase (20-30%)	-	1
<u>During Bronchoscopy</u>		
Decrease (20-30%)	-	3
Increase (20-30%)	-	2
Increase (30-50%)	-	3
Increase ($\geq$ 50%)	1	-
<u>During Recovery</u>		
Decrease (20-30%)	2	2
Decrease (30-50%)	2	-
Increase (20-30%)	1	4
Increase (30-50%)	3	-
Increase ($\geq$ 50%)	2	-

Summary and Conclusions

This randomized, double-blind study included 22 patients, and demonstrated that both midazolam and diazepam were effective intravenous sedative agents for bronchoscopy, when used as adjuncts to intramuscular meperidine and local anesthetic. Favorable assessments of sedation were given in most instances by the physician. Favorable ratings for sedation were given for both test medications by the patients with most indicating that they would elect to undergo the procedure the same way again. All patients reported little or no pain associated with the bronchoscopy.

There were no statistically significant differences between the treatments on the Trieger Test; however, one hour following the bronchoscopy the midazolam group had a greater impairment of psychomotor performance represented by both missed dots and deviation from the dots. With respect to amnesia, one hour after the bronchoscopy more midazolam than diazepam-treated patients would not recall the procedure. Most patients in both groups had lack of retrograde amnesia by the following day, while about half the patients had diminished recall of the procedure on the following day.

Induration was noted at the intravenous injection site of one midazolam patient. Two patients who received midazolam experienced deep sedation with hypotension or apnea which required treatment. One diazepam-treated patient had hypotension, but no treatment was necessary.

Midazolam was shown in this study to be a useful sedative agent when used in combination with meperidine and a topical anesthetic agent. It was comparable to diazepam with respect to effectiveness. Depression leading to apnea or hypotension occurred in several cases with these agents.

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Study No. 117

Title: A Comparison of Midazolam and Diazepam In Combination With Meperidine During Local Anesthesia for Bronchoscopy

Investigator: Oscar Balchum, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in adults undergoing bronchoscopy for the first time.

Experimental Design

Randomized, double-blind study in 21 adults undergoing bronchoscopy.

Prior to bronchoscopy midazolam or diazepam was administered by random coded assignment. Immediately following bronchoscopy, the physician, who was unaware as to which test medication had been administered, evaluated as excellent, good, fair or poor the sedative effects produced by the test medication. These assessments included: (1) patient cooperation, (2) muscle relaxation, (3) ease of bronchoscopic examination, (4) control of gag reflex, (5) control of laryngospasm, (6) control of bronchospasm, (7) control of cough reflex, (8) control of retching and vomiting, (9) control of salivation and (10) overall tolerance of the procedure. One hour after bronchoscopy and one day later in a follow-up questionnaire, patients evaluated the sedation during the procedure as excellent, good, fair or poor. Additionally, on both occasions, patients were asked whether they would elect to undergo a future bronchoscopy the same way, if necessary. One hour after bronchoscopy, patients evaluated the procedure as not painful, somewhat painful or very painful and whether they could recall none, some or all of the bronchoscopy. In the follow-up questionnaire, patients were also asked whether they could recall clearly, vaguely or not at all events before, during and after bronchoscopy.

Recovery from sedation was assessed by the Trieger Test which was completed by the patient before medication (baseline) and at 60 and 120 minutes following the completion of the bronchoscopy. Each Trieger Test was evaluated for the number of dots missed and the total deviation (mm) from the dots.

Blood pressure, respiratory rate and pulse rate were monitored before, during and after bronchoscopy. Changes in vital signs greater than 20% from baseline were identified as possible adverse experiences. The severity of these changes were categorized as:

mild = a change $\geq$ 20 percent but $<$ 30 percent from baseline
moderate = a change $\geq$ 30 percent by $<$ 50 percent from baseline
severe = a change $\geq$ 50 percent from baseline or treatment required.

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Clinical adverse experiences were further categorized according to the phase of the study. The phases of the study were defined as follows:

induction = period of test drug administration
maintenance = period of bronchoscopy
recovery = post-bronchoscopy until discharge

Seven to 14 days following the study, the intravenous injection site was examined for redness, tenderness and induration.

Subjects

There were 7 non-pregnant females and 14 males, ranging in age from 26 to 77 years. In the midazolam group there were 6 males and 4 females with a mean age of 44.0 years (range 26-72). In the diazepam group there were 8 males and 3 females with a mean age of 51.2 years (range 34-77).

Study Drugs

Thirty minutes before bronchoscopy, meperidine 50 mg and atropine 0.5 mg were administered intramuscularly to the patients. Following topical anesthetic administration, 5.0-7.5 mg of either midazolam or diazepam were administered intravenously over a 2-3 minute period. Elderly patients (as identified by the investigator) received 2.5-3.75 mg of the test medications. Incremental doses (25% in initial dose) were administered, if necessary, until the patient's speech became thickened and slurred but the patient was still responsive to verbal commands. When needed, additional doses were administered to maintain sedation.

Results

Deviations from Protocol

Two patients, one in each treatment group, were excluded from efficacy analyses. One patient _____ experienced hypotension and apnea 10 minutes after receiving midazolam (0.095 mg/kg). This patient required respiratory assistance and the administration of Narcan to reverse the effects of meperidine and midazolam. Bronchoscopy was cancelled. Recovery was complete in 45 minutes. Patient _____ who received diazepam (0.054 mg/kg), experienced laryngospasms due to edema from chronic bronchitis which forced the cancellation of the bronchoscopy.

Three patients did not answer questions on the 24-hour questionnaire:

(Midazolam) - Recall of two-hour Trieger Test
(Diazepam) - Recall of one and two-hour Trieger Test
____ (Diazepam) - Recall Baseline Trieger Test

000032

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.036 mg/kg of midazolam and 0.093 mg/kg of diazepam. An additional dose to maintain sedation was required by six midazolam-treated patients (22) and five diazepam-treated patients. The mean time required to reach the sedative end point (slurred speech) was similar in both groups (midazolam: 2.95 minutes, diazepam: 3.28 minutes) for similar mean duration of bronchoscopy.

Physician's Assessment of Sedation

The physician's assessment of sedation was in most instances "fair" to "excellent" for both midazolam and diazepam-treated patients. There were no significant differences between treatments in the physician's assessment of the test medications.

Patient's Assessment of Sedation

One hour after the procedure 8 of 9 midazolam patients and 9 of 10 diazepam patients rated the sedation as "good" or excellent, with one patient in each group rating it "fair." On the day following the procedure all patients rated the sedation produced by midazolam or diazepam as "good" or "excellent." Both groups reported the procedure as "somewhat painful" or "not painful," although 6 of 9 midazolam patients reported no pain versus 9 of 10 diazepam patients. Eight of nine midazolam patients indicated they would elect to undergo the procedure the same way again, one hour after the procedure as well as on the following day; while, 9 of 10 diazepam patients would elect the same method of sedation one hour after the procedure and 10 of 10, the following day.

Trieger Test

Diazepam-treated patients missed significantly more dots on the one and two-hour than did midazolam-treated patients. Total deviation from dots (mm) was also significantly greater among the diazepam-treated patients at the two-hour testing time.

Follow-up Questionnaire for Amnesia

There were no significant differences between treatments with respect to any of the recall questions. Recall of bronchoscopy was present in 1/9 midazolam patients and 4/10 diazepam patients.

Most patients, on the following day, had no retrograde amnesia as evidenced by recall of the baseline Trieger Test, the injection in the thigh and the spraying of the throat. Anterograde amnesia with respect to recall of scope introduction and withdrawal was induced in the majority of patients in both groups. This amnesia extended for two hours for 3/9 patients in the midazolam group and 5/10 patients in the diazepam group with respect to recall of the post-treatment Trieger Tests.

000033

G. Adverse Reactions

Severe Reactions

Patient - Midazolam

A 72 year old female with a history of hypertension developed hypotension and apnea 10 minutes after receiving 1.25 ml (0.095 mg/kg) of midazolam. The patient required artificial ventilation for 25 minutes. A drop in blood pressure from 190/100 mmHg to 130/80 mmHg was observed. Narcan was administered to reverse the hypotension induced by meperidine and midazolam. Recovery was complete within 45 minutes; however, the bronchoscopy was cancelled. The investigator attributed the hypotension and apnea to both the meperidine and midazolam.

Patient - Diazepam

A patient with chronic obstructive pulmonary disease experienced momentary apnea. This did not require any intervention; consequently, the procedure was successfully completed.

Patient - Midazolam

This patient displayed clenching of the jaws twice during the administration of a local anesthetic agent to the pharynx and once immediately following the intravenous injection of midazolam. After 1 1/2 to 2 minutes the jaws relaxed and the procedure could be continued. Since the clenching of the jaws was observed first before the administration of midazolam, the investigator felt that this was only remotely related to the administration of midazolam.

Patient - Diazepam

This patient experienced laryngospasm which prevented bronchoscopic passage, forcing cancellation of the bronchoscopy. The laryngospasm was felt to be caused by marked edema of the pharynx due to chronic bronchitis. There was no venous irritation in any patient at the time of follow-up examination.

Changes in Vital Signs

The following tables indicate in which phase of the study the changes in vital signs occurred and the severity of the changes. Most changes were mild to moderate and were most often associated with the bronchoscopy.

000034

Table 1

Changes From Baseline For Mean Arterial Pressure

	Number of Patients	
	Midazolam	Diazepam
<u>Number of Patients Studied</u>	10	11
<u>During Bronchoscopy</u>		
Decrease (20-30%)	1	-
Increase (20-30%)	3	1
Increase (30-50%)	-	2
<u>During Recovery</u>		
Decrease (20-30%)	2	1
Increase (20-30%)	1	2

Table 2

Changes From Baseline For Pulse Rate

	Number of Patients	
	Midazolam	Diazepam
<u>Number of Patients Studied</u>	10	11
<u>During Induction of IV Sedation</u>		
Increase (30-50%)	-	1
<u>During Bronchoscopy</u>		
Decrease (20-30%)	1	1
Increase (20-30%)	3	2
Increase (30-50%)	-	3
Increase ($\geq$ 50%)	2	1
<u>During Recovery</u>		
Decrease (20-30%)	3	1
Increase (20-30%)	1	1
Increase (30-50%)	-	-
Increase ($\geq$ 50%)	1	-

000035

Table 3

Changes From Baseline For Respiration Rate

<u>Number of Patients Studied</u>	<u>Number of Patients</u>	
	<u>Midazolam</u>	<u>Diazepam</u>
<u>During Induction of IV Sedation</u>	10	11
Decrease	-	1
<u>During Bronchoscopy</u>		
Decrease (20-30%)	-	2
Decrease (30-50%)	4	3
Decrease ($\geq$ 50%)	-	2
Increase (20-30%)	1	1
Increase (30-50%)	2	4
Increase ($\geq$ 50%)	2	1
<u>During Recovery</u>		
Decrease (20-30%)	3	1
Decrease (30-50%)	1	4
Increase (20-30%)	2	2
Increase (30-50%)	1	1
Increase ($\geq$ 50%)	1	-

Summary and Conclusions

Although this randomized, double-blind study only involved 21 patients, it demonstrated that midazolam and diazepam were both effective intravenous sedative agents for bronchoscopy, when used in combination with meperidine and a topical anesthetic agent. Favorable ratings for sedation were given by the physician and patients in both groups. Diazepam-treated patients had a significant increase in number of dots missed and total deviation from dots in the Trieger Test, indicating possible impairment of psychomotor performance following the procedure. Both agents were effective in producing retrograde amnesia and amnesia for scope manipulation.

Apnea and hypotension was experienced by a midazolam patient, and momentary apnea was experienced by one diazepam patient. There were no reports of irritation at the intravenous injection site at the follow-up examination. Most changes in vital signs were not clinically significant.

This study showed that midazolam, when used in combination with meperidine and a topical anesthetic agent was as safe and effective as diazepam in inducing sedation for bronchoscopy. It was as useful as diazepam in producing retrograde failure of recall and certain aspects of antegrade failure of recall.

000026

Study No. 118

Title: A Comparison of Midazolam and Diazepam In Combination With Meperidine During Local Anesthesia for Bronchoscopy

Investigator: Stephen Jenkinson, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in adults undergoing bronchoscopy for the first time.

Experimental Design

Randomized, double-blind study in 21 adults undergoing bronchoscopy. The design of this study was similar to that of study 117 since this was a multicenter study following the same protocol.

Subjects

There were 9 non-pregnant females and 12 males ranging in age from 27 to 70 years. In the midazolam group there were 5 males and 5 females with a mean age of 53.4 years (range 27-70). In the diazepam group there were 7 males and 4 females with a mean age of 48.3 years (range 33-67).

Study Drugs: See Study 117.

Results

Deviations from Protocol

Patients _____ who received midazolam, was excluded from all efficacy analyses since this was the second time a bronchoscopy had been done. This patient had been previously entered in the study as patient _____. This patient was included in all safety analyses.

One patient _____ who received midazolam could remember doing the Trieger Test only once following the bronchoscopy but did not know whether it was the one or two-hour test. The responses to recall of the Trieger Test, therefore, were not included in the analysis.

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.096 mg/kg of midazolam and 0.086 mg/kg of diazepam. The mean time to reach the sedative end point (slurred speech) was similar in both groups (midazolam: 3.94 minutes, diazepam; 4.58 minutes) for similar mean durations of bronchoscopy.

000037

Physician's Assessment of Sedation

The physician's assessment of sedation was in most instances "good" to "excellent" for both midazolam and diazepam-treated patients. Patients in the midazolam group had significantly better tolerance of the procedure than did patients in the diazepam group. There were no other significant differences between ten groups in the other assessments.

Patient's Assessment of Sedation

One hour after the procedure, all patients in the midazolam group rated the quality of sedation as "good" or "excellent" (9/9) which was significantly better than the rating by patients in the diazepam group (8/11) with 2 patients in this group rating "fair" and 1, "poor." There was no significant difference on the following day since two diazepam-treated patients changed their opinion of the quality of sedation from "fair" to "good." All of the midazolam and 9 of 11 diazepam patients indicated they would elect to undergo the procedure the same way again, one hour after the procedure as well as on the following day. Eight of nine midazolam patients reported no pain associated with bronchoscopy compared with 10 of 11 diazepam patients.

Trieger Test

There were no significant differences between groups in number of dots missed and total deviation from dots (mm).

Follow-Up Questionnaire for Amnesia

With respect to the questions for retrograde amnesia 3 of 9 midazolam patients and 11 of 11 diazepam patients had clear recall of the baseline Trieger Test. Five of 9 midazolam patients and 11 of 11 diazepam patients had clear recall of the injection in the thigh of meperidine. These differences were statistically significant and indicate more retrograde amnesia for midazolam patients. There was also some antegrade amnesia in midazolam patients since all but one did not have clear recall of scope introduction compared with only 3 of 11 diazepam patients. This difference was statistically significant. Four of 9 midazolam patients had antegrade amnesia extending to two hours with respect to failure to recall the post-treatment Trieger Test, compared with 1 of 11 diazepam patients.

Safety

Patient II - Diazepam A 67 years old male with a history of coronary artery disease experienced anginal pains at the end of the procedure. The pains were relieved by the administration of nitroglycerin.

No patient in either group had evidence of venous irritation at the follow-up examination.

000028

Changes in Vital Signs

The following table indicates in which phase of the study the changes in vital signs occurred and the severity of the changes. Most changes were associated with the bronchoscopy. No changes in vital signs were observed during the period of induction of sedation. Severe increases in respiration and pulse rate were observed in several patients in both treatment groups.

Table 1

Changes From Baseline For Vital Signs

<u>Number of Patients Studied</u>	<u>Number of Patients</u>	
	<u>Midazolam</u>	<u>Diazepam</u>
	10	11
<u>Respiration Rate</u>		
<u>During Bronchoscopy</u>		
Decrease (20-30%)	1	-
Decrease (30-50%)	-	1
Increase (20-30%)	-	4
Increase (30-50%)	-	2
Increase ($\geq$ 50%)	2	1
<u>During Recovery</u>		
Decrease (20-30%)	1	-
Increase (30-50%)	2	2
Increase ($\geq$ 50%)	2	2
<u>Pulse Rate</u>		
<u>During Bronchoscopy</u>		
Decrease (20-30%)	-	1
Increase (30-50%)	1	2
Increase ($\geq$ 50%)	1	1
<u>During Recovery</u>		
Decrease (20-30%)	1	1
Increase (20-30%)	1	2
Increase (30-50%)	-	1
Increase ($\geq$ 50%)	2	-
<u>Mean Arterial Pressure</u>		
<u>During Bronchoscopy</u>		
Increase (20-30%)	-	2

000030

Summary and Conclusions

This randomized, double-blind study in 21 patients demonstrated that midazolam and diazepam were both effective intravenous sedative agents for bronchoscopy, when used in combination with meperidine and a local anesthetic agent. Favorable ratings for sedation were given by the physician and patients in both groups. Most patients reported little or no pain associated with the bronchoscopy and were willing to undergo the procedure the same way again, if necessary. One hour following the procedure, quality of sedation was rated as significantly better by the midazolam patients.

Amnesia for certain events prior to drug administration (baseline Trieger Test, thigh injection) was significantly more frequently observed in the midazolam patients as was amnesia, after drug administration, for recall of scope introduction. Recovery from sedation as assessed by the Trieger Test was comparable between treatments.

Changes in vital signs were comparable between groups and were not felt to be clinically significant. At the follow-up examination, no patient had evidence of venous irritation. One diazepam patient, with a history of coronary artery disease, experienced anginal pains at the end of the procedure which were relieved by nitroglycerine.

Midazolam was shown in this study to be a useful sedative agent when used in combination with meperidine and a topical anesthetic agent. It was comparable to diazepam with respect to safety and effectiveness and was superior with respect to production of certain aspects of retrograde and anterograde amnesia.

000040

Study No. 123

Title: A Comparison of Midazolam and Diazepam In Combination With Meperidine During Local Anesthesia for Bronchoscopy

Investigator: William I. Mariencheck, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in adults undergoing bronchoscopy for the first time.

Experimental Design

Randomized, double-blind study in 24 adults undergoing bronchoscopy. The design of this study was similar to that of study 117 since this was a multicenter study following the same protocol.

Subjects

There were 12 non-pregnant females and 12 males ranging in age from 20 to 79 years. In the midazolam group there were 4 males and 7 females with a mean age of 48.1 years (range 25-72). In the diazepam group there were 8 males and 5 females with a mean age of 53.4 years (range 20-79).

Study Drugs: See Study 117.

Results

Deviations from Potocol

These patients were excluded from the efficacy analyses only.

Patient _____ - Diazepam: The drug was not administered according to protocol. 8 ml's of drug was given without using "slurred speech" as an index for dosage.

Patient _____ - Midazolam: Excludable concomitant medication (Asendin) was given within 24 hours of the procedure.

Patient _____ - Midazolam: Excludable concomitant medication (Valium) was given within 24 hours of the procedure.

There were only 11 diazepam-treated patients evaluated for amnesia since Patient _____ did not return the 24-hour follow-up questionnaire. This patient's Trieger Test results were also excluded from analysis since meperidine and atropine were administered before the baseline Trieger Test was done. Patient #8 of the midazolam group did not do the baseline Trieger Test; therefore, the post-treatment Trieger Test results were excluded from analysis.

000041

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.132 mg/kg of midazolam and 0.155 mg/kg of diazepam. The mean time to reach the sedative end point (slurred speech) was similar in both groups (midazolam: 3.06 minutes, diazepam: 2.58 minutes) for similar mean durations of bronchoscopy.

Physician's Assessment of Sedation

The physician's assessment of sedation was in most instances "good" to "excellent" in both treatment groups, with the exception of control of cough reflex which was rated "fair" to "good" in both groups. There were no statistically significant differences between treatments in the physicians assessment of the test medications.

Patient's Assessment of Sedation

On both assessment occasions (one hour after the procedure and on the following day) patients rated the quality of sedation significantly better than diazepam-treated patients. Both test groups reported little or no pain associated with the bronchoscopy.

All midazolam and most diazepam-treated patients indicated that they would elect to have a future bronchoscopy done the same way.

Trieger Test

There were no significant differences between groups in psychomotor recovery from sedation. Midazolam-treated patients returned to baseline values for number of dots missed and deviation from dots after two hours; whereas, diazepam-treated patients increased from their baseline values at both one and two hours.

Follow-Up Questionnaire for Amnesia

All patients in both groups recalled the baseline Trieger Test, the meperidine injection and the topical anesthetic spraying prior to bronchoscopy indicating lack of retrograde recall. Following intravenous drug administration, recall of the introduction and withdrawal of the bronchoscope was absent in all of the midazolam and all but 1 of the diazepam patients. The sponsor erroneously referred to the instrument used as a "cystoscope" on page 8 of the summary. Several patients in both groups could not recall the one-hour post-treatment Trieger Test. All patients could recall the two-hour post-treatment Trieger Test.

000012

Safety

Immediately following injection of midazolam patient experienced mild hiccoughs which subsided spontaneously after 15-30 seconds. Two midazolam patients experienced nausea following the bronchoscopy. One diazepam patient developed nausea and vomiting following the procedure while patient had nausea upon injection of diazepam. During injection of diazepam, four patients experienced pain. Only patient #20 had subsequent evidence of venous irritation (tenderness, redness) which subsided after 2 days. No treatment was required for any of the adverse experiences.

Changes in Vital Signs

The following table indicates in which phase of the study the changes in vital signs occurred and the severity of the changes. Most changes were mild to moderate and were most often associated with the bronchoscopy. Only one change occurred during induction. Patient who received midazolam had a mild increase in respiration rate.

Table 1

Changes From Baseline In Vital Signs

	Number of Patients	
	Midazolam	Diazepam
<u>Number of Patients Studied</u>	11	13
<u>Mean Arterial Pressure</u>		
<u>During Bronchoscopy</u>		
Decrease (20-30%)	1	-
Increase (20-30%)	1	3
<u>During Recovery</u>		
Decrease (20-30%)	-	1
Decrease (30-50%)	1	-
Increase (20-30%)	-	1
<u>Pulse Rate</u>		
<u>During Bronchoscopy</u>		
Decrease (20-30%)	-	4
Increase (30-50%)	1	4
Increase ($\geq$ 50%)	3	-

000042

Table 1 (Continued)

	<u>Number of Patients</u>	
	<u>Midazolam</u>	<u>Diazepam</u>
<u>Pulse Rate (Continued)</u>		
<u>During Recovery</u>		
Decrease (20-30%)	3	1
Increase (20-30%)	1	6
Increase (30-50%)	1	2
Increase ($\geq$ 50%)	2	-
<u>Respiration Rate</u>		
<u>During Induction</u>		
Increase (20-30%)	1	-
<u>During Bronchoscopy</u>		
Decrease (20-30%)	-	1
Decrease (30-50%)	1	-
Increase (20-30%)	1	3
Increase (30-50%)	1	1
Increase ($\geq$ 50%)	1	-
<u>During Recovery</u>		
Decrease (20-30%)	1	-
Decrease (30-50%)	1	2
Increase (20-30%)	1	2
Increase (30-50%)	1	1
Increase ($\geq$ 50%)	2	2

Summary and Conclusions

This randomized, double-blind study included 24 patients and demonstrated that both midazolam and diazepam were effective intravenous sedative agents for bronchoscopy when used as adjuncts to intramuscular meperidine and local anesthetic. Assessment of sedation by the physician was "good" to "excellent" for all parameters of both test medications except for control of cough reflex which was classified as "fair" to "good." Midazolam patients rated the quality of sedation significantly better than diazepam patients. All midazolam patients and diazepam patients indicated that they would elect to undergo the procedure the same way again.

Recall of the bronchoscopic procedure was absent in all of the midazolam and all but one of the diazepam patients. Both test groups showed some psychomotor impairment one hour following the bronchoscope. This persisted at the two-hour assessment in the diazepam-treated patients.

000044

Changes in vital signs were not felt to be clinically significant. Two patients in each group experienced nausea and one diazepam-treated patient also experienced vomiting. On injection of midazolam one patient experienced mild hiccoughs which promptly subsided. The investigator felt that the nausea, vomiting and hiccoughs were possibly related to the administration of midazolam and diazepam. No treatment was required for any adverse experiences. Four patients experienced pain upon injection of diazepam; however, only one of these patients had evidence of venous irritation (tenderness and redness) on the follow-up examination. No midazolam patients had evidence of venous irritation.

In this study midazolam was shown to be a useful sedative agent when used in combination with meperidine and a topical anesthetic agent. It was as safe and effective as diazepam in inducing sedation for bronchoscopy. The use of both agents was associated with diminished recall of the procedure.

Pooled Study Summary

Study No. 105, 113, 119, 150, Protocol 2236A

Title A Comparison of Midazolam and Diazepam Administered Intravenously With Local Anesthesia For Cystoscopy

Subjects

One hundred fifty-one patients (ASA Status I or II) undergoing diagnostic cystoscopy for the first time participated in the study. The study populations consisted of 42 non-pregnant females and 109 males ranging in age from 17 to 86 years. In the midazolam group there were 75 patients comprised of 54 males and 21 females with a mean age of 52.2 years (range 17-86). In the diazepam group there were 76 patients comprised of 55 males and 21 females with a mean age of 49.3 years (range 18-85).

ResultsDifferences Between Study Centers

There was a difference by centers in initial dose of the test drug for induction of sedation. In Dr. Evan's study (#113), patients receiving midazolam required a higher dose than did those who received diazepam. At the other three study sites the dose of diazepam was greater than midazolam.

There was a difference between study centers on the physician's assessment of sedation. Dr. Evans rated diazepam patients higher on all sedation parameters. The investigators at the other three centers either rated patients who received midazolam as better sedated or rated the sedative effects of the two test drugs as comparable.

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.152 mg/kg of midazolam and 0.170 mg/kg of diazepam. Two patients in Dr. Evan's study (one in each treatment group) required a maintenance sedation dose for completion of the procedure. The mean time to reach the sedative end point was 3.9 and 3.5 minutes respectively in the midazolam and diazepam groups. The mean length of the procedures was comparable between treatment groups.

Physician's Assessment of Sedation

There were no significant differences between treatments. All parameters were rated "good" to "excellent."

Patient's Assessment of Sedation

On two occasions patients assessed the sedative effects of the test drugs and whether they were willing to undergo a future procedure the same way. The two assessment periods were one hour after the procedure and on the following day. On both occasions quality of sedation was rated significantly better by midazolam-treated patients.

On both occasions ninety percent or more of the patients in both treatment groups were willing to have a future procedure done the same way. At the 24 hour interval significantly more midazolam patients were willing to have the procedure done the same way. They also reported significantly less pain associated with the cystoscopy.

Trieger Test

At one hour the increase in number of dots missed and deviations from the dots was significantly greater for patients treated with midazolam. By two hours both treatment groups had returned to near the baseline values.

Follow-up Questionnaire for Amnesia

While most patients could recall completing the baseline Trieger Test prior to test drug administration significantly more of the patients who received midazolam could not recall the administration of the local anesthetic agent.

Following test drug administration, one hour after the procedure, the diazepam group had little diminution in recall of cystoscopy; where, the midazolam group had significantly less recall. In this group there was also significantly less recall of the introduction and withdrawal of the scope as well recall of the one and two hour Trieger Tests, when questioned on the following day. Incidence of recall for the scope was much less than for the Trieger Tests.

Safety

Table 1

Clinical Adverse Experiences

<u>Possibly and Probably Related Drug Effects</u>	<u>Midazolam</u>		<u>Diazepam</u>	
	<u>No. Pts.</u>	<u>Percent</u>	<u>No. Pts.</u>	<u>Percent</u>
<u>Respiratory System</u>				
Respiration Rate Increase	15	20.0	14	18.4
Respiration Rate Decrease	12	16.0	8	10.5
Shallow Respiration	1	1.3	0	0
Apnea	1	1.3	3	3.9
<u>Cardiovascular System</u>				
Pulse Increase	12	16.0	12	15.8
Pulse Decrease	6	8.0	5	6.6
MAP Increase	3	10.7	3	3.9
MAP Decrease	12	16.0	4	5.3
Hypotension	0	0	1	1.3
Tenderness of Vein	3	4.0	1	1.3
Redness of Vein	1	1.3	0	0
Induration of Vein	2	2.7	1	1.3
<u>Miscellaneous</u>				
Excessive Sedation	1	1.3	0	0
<u>Remotely Related Effects</u>				
Arrhythmia	0	0	1	1.3

Changes in vital signs were observed more frequently during and following the cystoscopy than during induction of sedation. Most changes were classified as mild or moderate.

Summary and Conclusions

In this multicenter study the results of four randomized, double-blind, parallel group studies included 151 patients undergoing diagnostic cystoscopy for the first time. It was demonstrated that midazolam and diazepam were effective intravenous sedative agents for cystoscopy when used as adjuncts to local anesthetic. Sedation was achieved with mean doses of 0.152 mg/kg of midazolam and 0.170 mg/kg of diazepam in a mean time of less than 4 minutes for both treatment groups.

The physicians' assessment showed no intergroup difference, but the patients rated the quality of sedation significantly better and reported significantly less pain associated with the cystoscopy. Furthermore, significantly more midazolam patients were willing to have the procedure done the same way in the future.

The Trieger Test was used to assess the recovery from sedation. One hour after the procedure midazolam patients had significantly more impairment of psychomotor performance; however, by two hours both treatment groups were approaching complete recovery from the sedative effects of the drugs.

Midazolam patients had significantly less recall of the local anesthetic agent as well as recall of cystoscopy and recall of the postoperative Trieger Tests.

Four patients at one study Center (#150), one of whom received midazolam and three who received diazepam, experienced momentary apnea following induction of sedation. No corrective measures were required and all procedures were successfully completed.

One patient had shallow respiration after receiving midazolam (0.169 mg/kg). Another patient who received midazolam (0.134 mg/kg) experienced excessive sedation following the procedure.

One diazepam-treated patient developed hypotension which was attributed to the drug's sedative effects. Three midazolam patients and one diazepam patient had evidence of venous irritation on the follow-up examination.

This study showed that IV midazolam was safe as diazepam and was considered by the patients to be more effective than diazepam in inducing sedation for cystoscopy. Patients who received midazolam experienced less pain (not no pain, as stated by the sponsor) and had diminished recall of the procedure.

The physicians' assessment showed no intergroup difference, but the patients rated the quality of sedation significantly better and reported significantly less pain associated with the cystoscopy. Furthermore, significantly more midazolam patients were willing to have the procedure done the same way in the future.

The Trieger Test was used to assess the recovery from sedation. One hour after the procedure midazolam patients had significantly more impairment of psychomotor performance; however, by two hours both treatment groups were approaching complete recovery from the sedative effects of the drugs.

Midazolam patients had significantly less recall of the local anesthetic agent as well as recall of cystoscopy and recall of the postoperative Trieger Tests.

Four patients at one study Center (#150), one of whom received midazolam and three who received diazepam, experienced momentary apnea following induction of sedation. No corrective measures were required and all procedures were successfully completed.

One patient had shallow respiration after receiving midazolam (0.169 mg/kg). Another patient who received midazolam (0.134 mg/kg) experienced excessive sedation following the procedure.

One diazepam-treated patient developed hypotension which was attributed to the drug's sedative effects. Three midazolam patients and one diazepam patient had evidence of venous irritation on the follow-up examination.

This study showed that IV midazolam was safe as diazepam and was considered by the patients to be more effective than diazepam in inducing sedation for cystoscopy. Patients who received midazolam experienced less pain (not no pain, as stated by the sponsor) and had diminished recall of the procedure.

000019

Study No. 105

Title: A Comparison of Midazolam and Diazepam Administered Intravenously With Local Anesthesia for Cystoscopy

Investigator: Russell Lawson, M.D.

Objective: The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in patients undergoing cystoscopy for the first time.

Experimental Design

Randomized, double-blind study in 43 adults undergoing cystoscopy for the first time. The design of this study was similar to that of study 150 since this was a multicenter study following the same protocol.

Subjects

There were 24 non-pregnant females and 19 males ranging in age from 18 to 86 years. In the midazolam group there were 9 males and 13 females with a mean age of 49.6 years (range 18-86). In the diazepam group there were 10 males and 11 females with a mean age of 48.3 years (range 19-85).

Study Drugs See Study 150.

Results

Deviations from Protocol

Two patients who received diazepam were excluded from all efficacy analyses due to protocol violations. Both patients were ASA status III, while the protocol called for status I-II. Patient , a 77 year old male, received 0.062 mg/kg of diazepam. Patient , an 84 year old female, received 0.065 mg/kg of diazepam. No side effects were observed and these patients were included in all safety analyses.

Due to delays encountered during the induction period, the time to induction was not recorded for one patient in each treatment group. For patient the procedure was delayed after administration of 5 mg of diazepam due to difficulties with the cystoscope; therefore an additional 5 mg of drug was required to maintain sedation. In the case of patient following administration of 10 mg of midazolam, a slight increase in blood pressure was observed. The procedure was delayed while the patient was observed for several minutes; however, since adequate sedation was not reached, an additional 5 mg of midazolam was administered. One patient , who received 0.128 mg/kg of midazolam, could not do the one-hour Trieger Test due to excessive sedation.

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Induction of Intravenous Sedation

Comparable levels of sedation were obtained with mean doses of 0.117 mg/kg of midazolam and 0.131 mg/kg of diazepam. The average time required to reach the sedative end point (slurred speech) for midazolam and diazepam were 2.50 minutes and 3.90 minutes. The duration of cystoscopy was similar for both groups.

Physician's Assessment

The physician's assessment of sedation was in most instances "good" to "excellent" for patients in both groups. Muscle relaxation, control of bladder spasm and control of pain ratings were significantly better in the midazolam group.

Patient's Assessment

One hour following the cystoscopy, all patients rated the quality of sedation as "good" or "excellent." Significantly more midazolam-treated patients rated sedation as "excellent" compared with diazepam-treated patients. On the following day no significant difference between treatments was found since patients in both groups changed their evaluations. While midazolam-treated patients reported significantly less pain associated with the cystoscopy, all patients in both groups indicated they would elect to undergo the procedure the same way again, with the exception of the midazolam group one hour after the procedure, when 91% responded affirmatively.

Trieger Test

There were no statistically significant differences between groups with respect to recovery from sedation. Midazolam-treated patients had a higher number of dots missed and total deviations from the dots one hour following the cystoscopy. At two hours the results in both groups were returning toward the baseline values.

Follow-Up Questionnaire for Amnesia

One hour after the procedure, both treatment groups had diminished recall of the cystoscopy. Midazolam-treated patients had significantly less recall of the procedure. By the following day, the majority of patients in both groups had diminished recall of scope introduction and withdrawal; however, recall was less in the midazolam group.

While most patients could recall doing the baseline Trieger Test prior to test drug administration, 32% of the diazepam group and 59% of the midazolam group had no recall of the administration of local anesthesia. The majority of patients in both groups had recall of the post-treatment Trieger Tests.

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Safety

Patient a 66 year old male diabetic, experienced arrhythmias and a drop in blood pressure after receiving 0.142 mg/kg of diazepam. The patient was hypertensive before receiving diazepam and was still hypertensive following a drop in blood pressure from 192/127 mmHg to 171/104 mmHg. The drop in blood pressure was attributed to the sedative effects of diazepam. Since the arrhythmias were observed both before and during the cystoscopy, the investigator felt that the arrhythmias were remotely related to diazepam. No corrective treatment was required for either adverse experience. Patient #40, who received diazepam, experienced tenderness and redness at the injection site for 3 days following the study.

A 69 year old male experienced excessive sedation after receiving 0.134 mg/kg of midazolam. The investigator was unable to arouse the patient at one hour to do the Trieger Test except by painful stimuli.

Three midazolam-treated patient experienced venous irritation at the injection site following the study. Patient experienced tenderness, redness and induration for two days. Patient experienced tenderness for 5 days. Patient experienced tenderness and induration for 3 days.

Most changes in vital signs were transient and were most often associated with the cystoscopy. Few changes in vital signs were observed during induction.

Summary and Conclusions

This randomized, double-blind study compared the use of IV midazolam with IV diazepam to provide sedation during cystoscopy. These agents were used as adjuncts to local anesthesia provided by topical lidocaine. Assessment of sedation by the physician was "good" to "excellent" for both medications. No consistent difference was observed between groups with respect to patient assessment of the quality of sedation. Midazolam-treated patients reported significantly less pain associated with the procedure, but all patients in both groups indicated, by the following day, that they would undergo a future cystoscopy the same way. There were no significant differences between treatments on the Trieger Test, but midazolam patients had greater impairment of psychomotor performance one hour after the procedure.

Both groups of patients had diminished recall of the cystoscopy. One hour after the procedure the midazolam group had significantly less recall than the diazepam group; however, on the following day no significant differences between treatments were observed. The majority of patients in both groups had recall of the post-treatment Trieger Tests.

A 66 year old hypertensive diabetic patient experienced a drop in blood pressure after receiving diazepam. This drop was attributed to a sedative effect. The patient also experienced arrhythmias before and during the cystoscopy. The investigator felt the arrhythmias were remotely related to diazepam administration.

000051

Safety

Patient a 66 year old male diabetic, experienced arrhythmias and a drop in blood pressure after receiving 0.142 mg/kg of diazepam. The patient was hypertensive before receiving diazepam and was still hypertensive following a drop in blood pressure from 192/127 mmHg to 171/104 mmHg. The drop in blood pressure was attributed to the sedative effects of diazepam. Since the arrhythmias were observed both before and during the cystoscopy, the investigator felt that the arrhythmias were remotely related to diazepam. No corrective treatment was required for either adverse experience. Patient #40, who received diazepam, experienced tenderness and redness at the injection site for 3 days following the study.

A 69 year old male experienced excessive sedation after receiving 0.134 mg/kg of midazolam. The investigator was unable to arouse the patient at one hour to do the Trieger Test except by painful stimuli.

Three midazolam-treated patient experienced venous irritation at the injection site following the study. Patient experienced tenderness, redness and induration for two days. Patient experienced tenderness for 5 days. Patient experienced tenderness and induration for 3 days.

Most changes in vital signs were transient and were most often associated with the cystoscopy. Few changes in vital signs were observed during induction.

Summary and Conclusions

This randomized, double-blind study compared the use of IV midazolam with IV diazepam to provide sedation during cystoscopy. These agents were used as adjuncts to local anesthesia provided by topical lidocaine. Assessment of sedation by the physician was "good" to "excellent" for both medications. No consistent difference was observed between groups with respect to patient assessment of the quality of sedation. Midazolam-treated patients reported significantly less pain associated with the procedure, but all patients in both groups indicated, by the following day, that they would undergo a future cystoscopy the same way. There were no significant differences between treatments on the Trieger Test, but midazolam patients had greater impairment of psychomotor performance one hour after the procedure.

Both groups of patients had diminished recall of the cystoscopy. One hour after the procedure the midazolam group had significantly less recall than the diazepam group; however, on the following day no significant differences between treatments were observed. The majority of patients in both groups had recall of the post-treatment Trieger Tests.

A 66 year old hypertensive diabetic patient experienced a drop in blood pressure after receiving diazepam. This drop was attributed to a sedative effect. The patient also experienced arrhythmias before and during the cystoscopy. The investigator felt the arrhythmias were remotely related to diazepam administration.

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A 69 year old midazolam-treated patient experienced excessive sedation after the cystoscopy and was aroused with painful stimuli. This may have been age and dose-related (0.134 mg/kg).

One diazepam and three midazolam-treated patients experienced venous irritation at the injection site following the study. Transient changes in vital signs were noted in both groups but were not considered clinically significant.

This study showed that midazolam, when used in combination with a local anesthetic agent (lidocaine) is as safe and effective as diazepam in inducing sedation for cystoscopy. Midazolam treatment was associated with less procedural pain and less recall of the procedure after one hour.

Study No. 113

Title: A Comparison of Midazolam and Diazepam Administered Intravenously With Local Anesthesia for Cystoscopy

Investigator: Arthur T. Evans, M.D.

Objective: The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in patients undergoing cystoscopy for the first time.

Experimental Design

Randomized, double-blind study in 28 patients undergoing cystoscopy for the first time. Forty patients were required by the protocol and this is an interim report of an in-progress study. The design of this study was similar to that of study 150 since this was a multicenter study following the same protocol.

Subjects

There were 9 non-pregnant females and 19 males (ASA status I or II) ranging in age from 17 to 54 years. In the midazolam group there were 10 males and 3 females with a mean age of 32.2 years (range 17-54). In the diazepam group there were 9 males and 6 females with a mean age of 27.7 years (range 19-47).

Study Drugs: See study 150.

Results

Deviations from Protocol

A 19 year old male patient was excluded from efficacy analysis for receiving an excludable concomitant medication within 24 hours of the procedure. After receiving 0.169 mg/kg of diazepam, the patient admitted to having smoked some marijuana on the morning of the procedure. This patient was included in all safety analyses.

One midazolam-treated patient was only 17 years old which was a protocol deviation. This patient was, however, included in all efficacy and safety analyses.

The 24 hour questionnaires of two midazolam patients were not included in the efficacy analysis. Patient answered the questionnaire on the same day as the procedure. Patient did not return the questionnaire.

Several questions were not answered by three patients on the 24 hour questionnaire:

(midazolam) Recall One-hour Trieger Test
 (diazepam) Recall Two-Hour Trieger Test
 (This patient did not do the two-hour Trieger Test)
 (diazepam) Recall Two-Hour Trieger Test

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.209 mg/kg of midazolam and 0.175 mg/kg of diazepam. An additional dose to maintain sedation was required by one patient in each treatment group. Although there was no significant difference in the mean times required to reach the sedative end point, the midazolam group took almost twice as long. The duration of the cystoscopy was similar for both groups.

Physician's Assessment

The physician's assessment of sedation was "fair" to "excellent" for both midazolam and diazepam treatment groups. Control of bladder spasm and quality of sedation were rated significantly higher in the diazepam group.

Patient's Assessment

One hour after the procedure most patients in both treatment groups rated sedation as "good." On the following day significantly more patients in the midazolam group rated sedation as "excellent" or "good" than the diazepam-treated patients. Both treatment groups reported little or no pain associated with the procedure. Most patients in both groups would undergo the procedure the same way again.

Trieger Test

There were no significant differences between groups in recovery from sedation. Both groups had an increase from baseline in number of dots missed and total deviation from the dots one hour following cystoscopy. At two hours the results had returned close to the baseline value.

Follow-Up Questionnaire for Amnesia

All patients in both treatment groups could recall the baseline Trieger Test. Significantly more midazolam patients had no recall of local anesthesia. Midazolam-treated patients also had significantly less recall of the introduction and withdrawal of the cystoscope and the one hour post-treatment Trieger Test. There was no significant differences between groups in recall of the two hour Trieger Test.

Safety

A 33 year old female patient experienced shallow respiration 2 minutes after receiving 10 mg (0.169 mg/kg) of midazolam. She was given oxygen and breathing was assisted with an Ambu bag for 30 minutes. No additional complications were observed and the patient was able to leave the hospital at the end of the study procedure. The investigator felt that the shallow respiration was caused by the administration of too high a dose of midazolam to the patient.

Very few changes in vital signs were observed during the study. All changes were classified as mild or moderate and, with the exception noted above, were considered clinically insignificant.

No patient in either treatment group had evidence of venous irritation at the injection site following the study.

Summary and Conclusions

This randomized, double-blind study compared the use of IV midazolam with IV diazepam to provide sedation during cystoscopy. These agents were used as adjuncts to local anesthesia provided by topical lidocaine. This study was analyzed while still in progress and the interim report represents the results of the first 28 patients. As adjuncts to local anesthesia, both midazolam and diazepam were effective intravenous sedative agents for cystoscopy. Assessments of sedation by the physician were "fair" to "excellent" for all parameters. On the day following the procedure, quality of sedation was rated significantly better by midazolam-treated patients. All patients reported little or no pain associated with the cystoscopy and most patients in both groups were willing to undergo the procedure the same way again, if necessary.

Recovery from sedation as assessed by the Trieger Test was comparable between treatments, with both test groups showing psychomotor impairment one hour following cystoscopy and return toward baseline at two hours. Midazolam-treated patients had significantly less recall of local anesthetic administration as well as introduction and withdrawal of the cystoscope and the one hour post-treatment Trieger Test.

Most changes in vital signs were transient and were not considered clinically significant. One patient developed shallow respirations after receiving midazolam. Breathing was assisted and oxygen was administered. The shallow respiration was attributed to the administration of too high a dose of midazolam for this patient. There were no reports of venous irritation following the study.

This incomplete study demonstrated that midazolam, when used in combination with a local anesthetic agent, is as safe and effective as diazepam in inducing sedation for cystoscopy. It proved useful in producing diminished recall of the procedure.

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Patient's Assessment

One hour after the cystoscopy and on the following day, when patients assessed the quality of sedation, midazolam was judged significantly better. The midazolam patients found the procedure painless; however, 60 percent of the diazepam-treated patients found the procedure "somewhat painful" or "very painful." All midazolam and 85% of the diazepam-treated patients indicated that they would undergo the procedure the same way again.

Trieger Test

One hour after cystoscopy, midazolam patients had a statistically significant increase in number of dots missed and total deviation from the dots compared with the diazepam group. No significant difference between treatments was observed for the two hour test results.

Follow-Up Questionnaire for Amnesia

On the follow-up questionnaire, midazolam-treated patients had significantly less recall for all events of the procedure, with the exception of the baseline Trieger Test, than did diazepam-treated patients. Significantly more midazolam-treated patients had no recall of the introduction and withdrawal of the cystoscope and of the one and two hour post-treatment Trieger Tests. Most diazepam-treated patients had recall of all events before and after test drug administration.

Safety

The only adverse experiences reported were mild to moderate changes in pulse rate and mean arterial pressure. No changes in vital signs were observed during induction of intravenous sedation. No patient in either group had evidence of venous irritation on the follow-up examination.

Summary and Conclusions

This randomized double-blind study compared the use of IV midazolam with IV diazepam to provide sedation during cystoscopy. These agents were used as adjuncts to local anesthesia provided by topical lidocaine. As Adjuncts to local anesthesia both midazolam and diazepam were effective intravenous sedative agents for cystoscopy. Assessments of sedation by the physician were in most instances "good" to "excellent" for both test medications. The quality of sedation was rated significantly better by midazolam patients. No midazolam-treated patients found the cystoscopy painful compared to the diazepam group, where 60% experienced some pain during the cystoscopy. All midazolam and most diazepam patients indicated they would elect to undergo the procedure the same way again.

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On the one hour Trieger Test, midazolam-treated patients had a statistically significant increase in number of dots missed and total deviation from the dots compared with the diazepam group, suggesting impairment of psychomotor performance. At two hours, the changes returned to near the baseline values. Failure of recall of events immediately prior to and following test drug administration was induced in most midazolam-treated patients, while most diazepam-treated patients could recall all of these events.

Transient fluctuations in blood pressure and pulse rate were noted, but were not felt to be clinically significant. There were no reports of venous irritation on the follow-up examination.

This study demonstrated that midazolam, when used in combination with a local anesthetic is as safe and effective as diazepam in inducing sedation for cystoscopy. Midazolam was more effective in inducing diminished recall of the procedure and other events before and after the procedure.

Study No. 150

Title: A Comparison of Midazolam and Diazepam Administered Intravenously with Local Anesthesia for Cystoscopy

Investigator: George Chasapakis, M.D.

Objective: The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in patients undergoing cystoscopy for the first time.

Experimental Design:

Randomized, double-blind study in 40 adults undergoing cystoscopy for the first time. Patients were randomly assigned to midazolam and diazepam treatment groups. Approximately 5 to 10 minutes before cystoscopy, lidocaine topical jelly was instilled into the urethra. Following this, 10-15 mg of either midazolam or diazepam was administered intravenously. Immediately following cystoscopy, the blinded physician, evaluated as excellent, good, fair or poor the sedative effects produced by the test medication. The assessments included: (1) patient cooperation, (2) muscle relaxation, (3) ease of cystoscopic examination, (4) quality of sedation, (5) control of bladder spasm, (6) control of pain, (7) control of retching and vomiting, (8) overall tolerance of the procedure. One hour after cystoscopy and one day later in a follow-up questionnaire, patients evaluated the sedation during the procedure as excellent, good, fair or poor. On both occasions patients were asked whether they would elect to undergo a future cystoscopy the same way. One hour after the procedure, patients evaluated the cystoscopy as not painful, somewhat painful or very painful and whether they could recall none, some or all of the cystoscopy. In the follow-up questionnaire, patients were also asked whether they could recall clearly, vaguely or not at all events before, during and after cystoscopy.

Recovery from sedation was assessed by the Trieger Test which was completed by the patient before medication (baseline) and at 1 and 2 hours after cystoscopy.

Blood pressure, respiratory rate and pulse rate were monitored before, during and after cystoscopy. Changes in vital signs greater than 20 percent from baseline were identified as possible adverse experiences. The severity of the change was categorized as follows:

Mild = a change $\geq$ 20 percent by $<$ 30 percent from baseline
Moderate = a change $\geq$ 30 percent but $<$ 50 percent from baseline
Severe = a change $\geq$ 50 percent from baseline or treatment required

Clinical adverse experiences were further categorized according to the phase of the study. The phases of the study were defined as follows:

induction = period of test drug administration
maintenance = period of cystoscopy
recovery = post cystoscopy until discharge.

N-18654-3

000056

Study No. 119

Title: A Comparison of Midazolam and Diazepam Administered Intravenously With Local Anesthesia For Cystoscopy

Investigator: Alan J. Wein, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in patients undergoing cystoscopy for the first time.

Experimental Design

Randomized, double-blind study in 40 patients undergoing cystoscopy for the first time. The design of this study was similar to that of study 150 since this was a multicenter study following the same protocol.

Subjects

There were 40 males ranging in age from 40 to 76 years (ASA Studies I and II). In the midazolam group there were 20 patients with a mean age of 61.0 years (range 20-75). In the diazepam group there were 20 patients with a mean age of 55.7 years (range 34-76).

Study Drugs

See Study 150.

Results

Deviations from Protocol

One midazolam-treated patient did not understand the directions for the Trieger Test; therefore, this patient's data were not included in the Trieger Test analysis. Patient of the midazolam group was unable to complete the one-hour Trieger Test because of excessive sedation.

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.118 mg/kg of midazolam and 0.140 mg/kg of diazepam. The mean time required to reach the sedative end point and the duration of cystoscopy were similar for both groups.

Physician's Assessment

The physician's assessment of sedation was in most instances "good" to "excellent" for both midazolam and diazepam-treated patients. The assessment of control of pain was significantly better for those patients who received midazolam. There were no statistically significant differences between treatments in the other assessments made by the physician.

Subjects

There were 9 non-pregnant females and 31 males ranging in age from 18 to 79 years (ASA Status I and II). In the midazolam group there were 15 males and 5 females with a mean age of 59.3 years (range 20-79). In the diazepam group there were 16 males and 4 females with a mean age of 60.1 years (range 18-76).

Study Drugs

Before cystoscopy, lidocaine topical jelly was instilled into the urethra. Following this, 10-15 mg of either midazolam or diazepam was administered intravenously over a 2-3 minute period. Elderly patients (as identified by the investigator) received 5-7.5 mg of the test medications. Incremental doses (25% of initial dose) were administered, if necessary, until the patient's speech became thickened and slurred but the patient was still responsive to verbal commands.

The formulation used in this study was not supplied by Hoffman-LaRoche, Nutley; however, it was a midazolam free base in a hydrochloric acid formulation. It was supplied by the company's Busle headquarters and appears to differ in that there is no edetate disodium in the formulation. In the opinion of this reviewer the formulations are not significantly dissimilar from a medical viewpoint.

Results

Deviations from Protocol

The seven to fourteen day follow-up examination of the intravenous injection site for tenderness, redness, or induration was not done on any patient in this study. One midazolam patient did not return the 24 hour patient questionnaire. Patient , who received diazepam (0.365 mg/kg) was extremely sleepy one hour following the procedure. This patient was unable to answer the one-hour questionnaire and to complete the one-hour Trieger Test. The physician did not answer the question of quality of sedation for patient of the diazepam group. Diazepam patient did not answer the question of pain associated with the cystoscopy.

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.164 mg/kg of midazolam and 0.234 mg/kg of diazepam. The respective mean times to reach the sedative end point (slurred speech) for midazolam and diazepam were 2.43 minutes and 3.03 minutes the average duration of the cystoscopies was similar for both groups.

Patients in both treatment groups performed well on their post-treatment Trieger Tests; however, diazepam-treated patients had a statistically significant increase in deviation from the dots at two hours compared with midazolam patients. While the majority of patients could recall the baseline Trieger Test, many could not recall the administration of local anesthesia. Failure to recall the introduction of the scope was induced in all of the midazolam patients and 95% of the diazepam patients. Failure to recall the withdrawal of the scope was induced in all patients.

Many patients experienced prolonged amnesia as they could not recall the one-hour post-treatment Trieger Test; however, most could recall the two-hour post-treatment test.

On midazolam and three diazepam-treated patients experienced momentary apnea following induction of sedation. However, since no corrective measures were required, all procedures were successfully completed. Transient changes in vital signs were observed in both treatment groups but were not felt to be clinically significant.

This study showed that midazolam, when used in combination with a local anesthetic agent, is as safe and effective as diazepam in inducing sedation for cystoscopy. Both midazolam and diazepam appear to be effective agents for inducing amnesia of the procedure.

Physician's Assessment

The physician's assessment of sedation was in most cases "good" to "excellent" for both midazolam and diazepam treatment groups. There were no statistically significant differences between treatments in the physician's assessment of the test medications.

Patient's Assessment

On two occasions (one hour after the procedure and the following day) most patients rated the sedation produced by both drugs as "good" or "excellent." Most patients in both groups reported little or no pain associated with the cystoscopy. Most patients were willing to undergo the procedure the same way again.

Trieger Test

Recovery from sedation was characterized in general by the fact that neither treatment group missed many dots or deviated far from the dots on the Trieger Test. At two hours, however, diazepam-treated patients had a statistically significant increase in deviation from the dots at two hours compared with midazolam-treated patients.

Follow-up Questionnaire for Amnesia

While almost all patients could recall the baseline Trieger Test, about half of the patients in both groups had no recall of local anesthesia administration. Most midazolam and diazepam-treated patients had no recall of the introduction and withdrawal of the introduction and withdrawal of the cystoscope on the following day, although one hour after the procedure most patients did recall the cystoscopy, with recall being greater in the diazepam group (55% vs. 79%). Most patients could recall the two-hour post treatment Trieger Test, although fewer patients in each group recalled the one-hour test.

Safety

One midazolam-treated patient _____ (.161 mg/kg) and three diazepam-treated patients _____ experienced apnea for 10-15 seconds following induction of sedation. No patient required corrective treatment and all cystoscopies were successfully completed. No changes in vital signs were observed during induction of sedation and all changes were classified as mild or moderate.

Summary and Conclusions

This randomized, double-blind study compared the use of IV midazolam with IV diazepam to provide sedation during cystoscopy. These agents were used as adjuncts to local anesthesia provided by topical lidocaine. Assessments of sedation by the physician and patient were "good" to "excellent" for both test medications. Most patients reported little or no pain associated with the procedure.

000083

Pooled Study Summary

Study Nos. 116, 126, Protocol 2237A

Title: A Comparison of Midazolam and Diazepam in Combination With Meperidine During Local Anesthesia for Cystoscopy

Subjects

There were fifty female patients (ASA Status I or II) ranging in age from 21 to 88 undergoing diagnostic cystoscopy for the first time. There were 12 females in the midazolam group with a mean age of 52.4 years (range 28-88) and 13 in the diazepam group with a mean age of 45.4 years (range 21-80). In the midazolam placebo groups there were 13 females with a mean age of 45.1 years (range 21-72) and in the diazepam placebo groups there were 12 females with a mean age of 50.3 years (range 27-79).

Results

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.090 mg/kg of midazolam and 0.092 mg/kg of diazepam. Two midazolam and three diazepam-treated patients required a maintenance dose for completion of the procedure. The mean time to reach the sedative end points for both active drug groups was less than 3 minutes.

Physician's Assessment

The assessment for midazolam-treated patients was "excellent" for all parameters while assessments in the other groups ranged from "poor" to "excellent". Midazolam-treated patients were rated significantly better than placebo (midazolam) and diazepam patients on all assessments except for control of retching and vomiting.

Patient's Assessment

One hour after the procedure, midazolam-treated patients evaluated sedation as significantly better and reported significantly less pain during the procedure than did placebo (midazolam) patients. No other significant differences were noted.

Trieger Test

Midazolam-treated patients missed significantly more dots on the one and two hour Trieger Tests and had a significant increase in deviation from the dots at one hour compared with diazepam and placebo (midazolam) patients.

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Follow-Up Questionnaire for Amnesia

Significantly fewer midazolam-treated patients could recall receiving local anesthetic than placebo (midazolam) and diazepam patients. One hour after cystoscopy, significantly fewer midazolam than placebo patients had recall of the procedure and this difference was also true on the following day for not only placebo, but also for diazepam versus midazolam. The difference was extended through the two hour Trieger Test for midazolam and placebo.

Safety

One diazepam and one placebo (midazolam) patient experienced tenderness (burning) at the intravenous injection site during administration of the test drug. Neither patient had evidence of irritation at the injection site at the follow-up examination. One placebo (midazolam) patient experienced dizziness following premedication with meperidine. Transient changes in vital signs were observed in all four treatment groups. No changes were observed during induction of sedation. All changes were classified as mild or moderate. None of the changes were clinically significant.

Summary and Conclusions

In this pooled study at one center midazolam was used to provide sedation during cystoscopy. It was compared to diazepam and placebo when administered intravenously as an adjunct to meperidine and a topical anesthetic agent.

Comparable levels of sedation were attained with mean doses of 0.090 mg/kg of midazolam and 0.092 mg/kg of diazepam. The mean time to induce sedation was similar and under 3 minutes for both active treatment groups.

Midazolam was a more effective sedative agent than diazepam and placebo (midazolam) and was rated significantly better on all the physician's assessments except control of retching and vomiting.

Patients who received midazolam evaluated quality of sedation as significantly better and reported significantly less pain associated with the cystoscopy than did placebo (midazolam)-treated patients. There were no significant differences between the active treatments on these parameters.

Midazolam-treated patients apparently had residual sedative effects during the one and two hour Trieger Tests since they missed significantly more dots compared with diazepam-treated patients.

Failure of recall of the procedure was significantly greater for the midazolam than for the diazepam group as was failure to recall local anesthesia prior to induction.

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Follow-Up Questionnaire for Amnesia

Significantly fewer midazolam-treated patients could recall receiving local anesthetic than placebo (midazolam) and diazepam patients. One hour after cystoscopy, significantly fewer midazolam than placebo patients had recall of the procedure and this difference was also true on the following day for not only placebo, but also for diazepam versus midazolam. The difference was extended through the two hour Trieger Test for midazolam and placebo.

Safety

One diazepam and one placebo (midazolam) patient experienced tenderness (burning) at the intravenous injection site during administration of the test drug. Neither patient had evidence of irritation at the injection site at the follow-up examination. One placebo (midazolam) patient experienced dizziness following premedication with meperidine. Transient changes in vital signs were observed in all four treatment groups. No changes were observed during induction of sedation. All changes were classified as mild or moderate. None of the changes were clinically significant.

Summary and Conclusions

In this pooled study at one center midazolam was used to provide sedation during cystoscopy. It was compared to diazepam and placebo when administered intravenously as an adjunct to meperidine and a topical anesthetic agent.

Comparable levels of sedation were attained with mean doses of 0.090 mg/kg of midazolam and 0.092 mg/kg of diazepam. The mean time to induce sedation was similar and under 3 minutes for both active treatment groups.

Midazolam was a more effective sedative agent than diazepam and placebo (midazolam) and was rated significantly better on all the physician's assessments except control of retching and vomiting.

Patients who received midazolam evaluated quality of sedation as significantly better and reported significantly less pain associated with the cystoscopy than did placebo (midazolam)-treated patients. There were no significant differences between the active treatments on these parameters.

Midazolam-treated patients apparently had residual sedative effects during the one and two hour Trieger Tests since they missed significantly more dots compared with diazepam-treated patients.

Failure of recall of the procedure was significantly greater for the midazolam than for the diazepam group as was failure to recall local anesthesia prior to induction.

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Transient fluctuations in vital signs were observed in all treatment groups but were not considered clinically significant. One diazepam and one placebo (midazolam)-treated patient experienced pain during the injection of the study drug. There were no reports of irritation at the intravenous injection site at the follow-up examination.

This study shows that midazolam, when used in combination with meperidine and lidocaine anesthetic, is as safe as diazepam in inducing sedation for cystoscopy. In this study the physician found midazolam to be a superior sedative agent and midazolam patients had more impairment of recall of the procedure and a pre-induction event than the diazepam group.

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Study No. 116

Title: A Comparison of Midazolam and Diazepam in Combination With Meperidine During Local Anesthesia for Cystoscopy

Investigator: Roy Witherington, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in 40 adult females undergoing cystoscopy for the first time.

Subjects

The study population consisted of 40 non-pregnant females (ASA Status I or II) ranging in age from 21 to 88 years. There were 10 females in each of 4 groups composed as follows:

1. Midazolam- mean age 52.4 years (range 28-88)
2. Diazepam- mean age 48.6 years (range 21-80)
3. Placebo (midazolam)- mean age 45.6 years (range 21-72)
4. Placebo (diazepam)- mean age 51.5 years (range 27-79)

Study Drugs

Approximately 30 minutes before cystoscopy, all patients received 25-50 mg of meperidine administered intramuscularly followed by the instillation of lidocaine topical jelly into the urethra 5 to 10 minutes prior to cystoscopy. Patients assigned to midazolam or diazepam treatment groups received 5.0-7.5 mg of the test medications intravenously over a 2-3 minute period. Elderly patients (as identified by the investigator) received 2.50-3.75 mg of the test medications intravenously over a 2-3 minute period. Incremental doses (25% of initial dose) were administered, if necessary, until the patient's speech became thickened and slurred but the patient was still responsive to verbal commands. Patients assigned to placebo groups received 1-3 ml total volume of solution administered intravenously over a 5 minute period.

Experimental Design

Immediately following cystoscopy, the blinded physician evaluated as excellent, good, fair or poor the sedative effects produced by the test medication. The assessments included: (1) patient cooperation, (2) muscle relaxation, (3) ease of cystoscopic examination, (4) quality of sedation, (5) control of bladder spasms, (6) control of pain, (7) control of retching and vomiting, and (8) overall tolerance of the procedure. One hour after

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cystoscopy and one day later in a follow-up questionnaire, patients evaluated the sedation during the procedure as excellent, good, fair or poor. In addition, on both occasions, patients were asked whether they would elect to undergo a future cystoscopy the same way, if necessary. One hour after cystoscopy, patients evaluated the procedure as not painful, somewhat painful or very painful and whether they could recall none, some or all of the procedure. One day later in the follow-up questionnaire, patients were also asked whether they could recall clearly, vaguely or not at all events before, during and after cystoscopy.

Recovery from sedation was assessed by the Trieger Test which was completed by the patient before medication (baseline) and at 60 and 120 minutes following the completion of the cystoscopy. Each Trieger Test was evaluated for the number of dots missed and the total deviations (mm) from the dots.

Vital signs were monitored before, during and after cystoscopy. Changes in vital signs greater than 20% from baseline were identified as possible adverse experiences. The severity of the change was categorized as:

mild = a change $\geq$ 20% but $<$ 30% from baseline
moderate = a change $\geq$ 30% but $<$ 50% from baseline
severe = a change $\geq$ 50% from baseline or treatment required

Clinical adverse experiences were further categorized according to the phase of the study, as induction, maintenance (cystoscopy) and recovery. Seven to 14 days following the study, the intravenous injection site was examined for tenderness, redness, and induration.

Results

Deviations from Protocol

No data were reported for the physician's assessment of control of pain for patient _____ of the placebo (midazolam) group. Patient _____ of the placebo (diazepam) group did not answer the questions regarding: quality of sedation and a future procedure done the same way on the 24 hour questionnaire.

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.089 mg/kg of midazolam and 0.089 mg/kg of diazepam. Two midazolam-treated patients _____ and three diazepam-treated patients _____ required maintenance sedation doses to complete the cystoscopy. The mean time required to reach the

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sedative end point was comparable between midazolam and diazepam treatment groups.

Physician's Assessment

The physician's assessments of sedation for midazolam patients were "excellent" for most parameters. The assessments for patients who received diazepam, and both placebos ranged from "poor" to "excellent". Patients who received midazolam were evaluated as significantly better than placebo patients for muscle relaxation, ease of cystoscopic examination, quality of sedation, control of bladder spasms, and control of pain. Midazolam patients were rated significantly better than diazepam patients for quality of sedation, control of pain, control of bladder spasm and control of retching and vomiting. Patients who received placebo had significantly better control of retching and vomiting than did diazepam patients.

Patient's Assessment

One hour after the procedure, midazolam patients rated sedation significantly better than patients who received placebo. On the following day, both midazolam and placebo (diazepam)-treated patients evaluated sedation significantly better than diazepam-treated patients. Midazolam patients experienced significantly less pain associated with the cystoscopy than did placebo (midazolam) and diazepam-treated patients. There were no significant differences between groups for patients who were willing to have a future cystoscopy done the same way.

Trieger Test

Midazolam patients missed significantly more dots on the one hour Trieger Test than did diazepam and placebo treated patients. Midazolam patients also had a significant increase in deviation from the dots when compared with placebo (midazolam) treated patients on the one hour Trieger Test. At two hours there were no significant differences between any of the treatment groups.

Follow-Up Questionnaire for Amnesia

Only 40% of the midazolam patients could recall receiving the local anesthetic. Failure to recall the procedure was induced in most midazolam patients and was extended to two hours in many, since they could not recall the post-treatment Trieger Tests. There was significantly less procedural recall for midazolam than placebo as well as recall of the one hour Trieger Test. There was also significantly less recall of the scope withdrawal in the midazolam group compared with the diazepam group.

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Safety

One diazepam patient and one placebo (midazolam)-treated patient experienced tenderness (burning) at the injection site during administration of the test drug. Neither of these patients had evidence of irritation at the injection site on the follow-up examination.

Patient experienced dizziness 45 minutes after receiving meperidine but prior to the administration of placebo (midazolam). The dizziness, therefore, was remotely related to the administration of placebo (midazolam).

Most changes in vital signs were transient and were not considered clinically significant. No changes were observed during induction of sedation. All changes were classified as mild or moderate.

Summary and Conclusions

This was a randomized, double-blind study. It compared the use of intravenous midazolam with oral diazepam and placebo as an adjunct to intramuscular meperidine and topical anesthetic administration to provide sedation for cystoscopy. For the physician's and patient's assessments, midazolam-treated patients experienced significantly more sedation than diazepam and placebo (midazolam)-treated patients. Midazolam patients also reported significantly less pain associated with the cystoscopy than did patients in the diazepam and placebo treatment groups. Since the dose of diazepam received by most patients was somewhat low, most diazepam-treated patients probably did not reach the optimal sedation level.

Midazolam patients missed significantly more dots on the one hour Trieger Test than did diazepam and placebo patients and had a significant increase in deviation from the dots when compared with placebo (midazolam) patients. This suggests impairment of psychomotor performance; however, by two hours the results had returned toward the baseline value. Retrograde and anterograde failure of recall was induced in many patients who received midazolam.

Transient fluctuations in vital signs were observed in all treatment groups but were not considered clinically significant. One diazepam and one placebo (midazolam) treated patient experienced burning during the injection of the study drug. There were no reports of irritation at the intravenous injection site on follow-up.

This study showed that I.V. midazolam when used in combination with meperidine and a topical anesthetic agent is as safe as diazepam in inducing sedation for cystoscopy. It appeared to be more effective than diazepam in producing sedation but this may have resulted because of low doses of diazepam.

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Study No. 126

Title: A Comparison of Midazolam and Diazepam in Combination With Meperidine During Local Anesthesia for Cystoscopy

Investigator: Roy Witherington, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in 40 adult females undergoing cystoscopy for the first time.

Subjects

The study population consisted of 10 females (ASA Status I or II) who were not pregnant and ranged in age from 22 to 62 years. Although 40 patients were projected for this study, it was still in progress at the time of submission. There were 2 females in the midazolam group with a mean age of 52.5 years (range 43-62), 3 in the diazepam group with a mean age of 34.7 years (range 28-39), 3 in the placebo (midazolam) group with a mean age of 43.3 years (range 22-61) and 2 in the placebo (diazepam) group with a mean age of 44.5 years (range 42-47).

Study Drugs: See Study 116

Experimental Design: See Study 116

Results

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.093 mg/kg of midazolam and 0.108 mg/kg of diazepam. Mean times to sedation were 2.2 minutes for midazolam and 3.4 minutes for diazepam.

Physician's Assessment

The assessments for all parameters were "excellent" for midazolam and "fair" to "excellent" for diazepam.

Patient's Assessment

Quality of sedation was rated "good" to "excellent" in both active treatment groups. All patients in these two groups stated that they would undergo a future cystoscopy the same way and all indicated that the procedure was either slightly or not painful.

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Trieger Test

Psychomotor recovery assessment demonstrated an elevation at one hour in both parameters in the midazolam group with return toward baseline at two hours. There was essentially no change in the diazepam scores at either 1 or 2 hours.

Follow-Up Questionnaire for Amnesia

There was no recall of cystoscopy in the midazolam group; whereas, in the diazepam group while no recall of the procedure was present 1 hour later, after 24 hours 2 of 3 patients had clear recall. One patient of 2 in the midazolam group recalled pre-induction procedures whereas in the diazepam group all 3 patients recalled at least 1 pre-induction event.

Safety

The only adverse experiences noted were transient changes in pulse rate and blood pressure. No changes were observed during induction of sedation. All changes were mild or moderate. No patient had evidence of venous irritation.

Summary and Conclusions

This was a randomized, double-blind study which was still in progress at the time of submission. Because only 10 of 40 patients were studied at the time, a statistical analysis of the results was not feasible.

Transient fluctuations in blood pressure and pulse rate were observed but were not considered clinically significant. No patient had evidence of venous irritation following the study.

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Pooled Study Summary

Study Nos. 124, 125, 127, 128, Protocol 2237B

Title: A Comparison of Midazolam and Diazepam In Combination With Meperidine During Local Anesthesia for Cystoscopy

Subjects

Ninety-five males (ASA I or II) undergoing diagnostic cystoscopy for the first time participated in the study. The study population ranged in age from 18 to 96 years. In the midazolam group there were 24 males with a mean age of 60.0 years (range 18-96). In the diazepam group there were 23 males with a mean age of 53.6 years (range 20-78). In the respective placebo groups there were 24 males each, with mean ages of 58.0 years (range 25-82) and 53.4 years (range 24-78).

Results

Differences Among Study Centers

There were no major differences between study centers.

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.104 mg/kg of midazolam and 0.145 mg/kg of diazepam. Midazolam-treated patients required a significantly shorter mean time to reach the sedative end point of 4.2 minutes compared with 5.7 minutes for diazepam patients.

Physician's Assessment

On all of the assessment parameters, midazolam's sedative properties were rated better than placebo. There were no significant differences between the active treatment groups.

Patient's Assessment

On both rating occasions, (one hour after the procedure and on the following day) the active treatment groups rated quality of sedation better than their corresponding placebo groups. On the following day, significantly more midazolam-treated patients stated they would undergo a future procedure the same way than placebo patients. Midazolam-treated patients reported significantly less pain associated with the procedure than patients who received diazepam.

Trieger Test

Both active treatment groups had significantly increased values over baseline in number of dots missed, at one hour, than their corresponding placebo

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groups. Additionally the diazepam group had a significantly elevated total deviation from dots compared with the corresponding placebo group. At two hours no significant differences existed between groups.

Follow-Up Questionnaire for Amnesia

Following test drug administration, both active test groups had diminished recall of the procedure. One hour after cystoscopy midazolam-treated patients had significantly less recall of the procedure compared with diazepam patients. Midazolam-treated patients also had significantly less recall than placebo patients of all events following test drug administration, including the introduction and withdrawal of the cystoscope and the one and two hour post-treatment Trieger Tests.

Patients who received diazepam had significantly less recall of the procedure and of the introduction of the cystoscope compared with placebo patients.

There were some patients in the various groups (more in the active drug groups) who could not recall the administration of the local anesthetic agent.

Safety

Two midazolam and one diazepam patients experienced excessive sedation during or following the procedure. In two cases the investigator felt that the excessive sedation was due to premedication with meperidine. All three patients were given test drug doses that were lower than the mean sedation dose.

One midazolam patient with arteriosclerotic heart disease became unresponsive to painful stimuli and hypotensive, responding to treatment with Narcan.

One midazolam-treated patient developed venous irritation at the injection site for 2 days following the study. A second patient experienced burning and stinging during the injection of midazolam. When the injection was slowed there were no further complaints. Tenderness was observed at the injection site for one day in one placebo (midazolam) patient.

Most changes in vital signs were observed during the maintenance and recovery. Most changes were classified as mild to moderate and were not clinically significant.

Summary

In this multicenter study midazolam when used in combination with meperidine and a topical anesthetic agent was shown to be as safe and effective as diazepam in inducing sedation for cystoscopy. Midazolam-treated patients reported significantly less pain associated with the procedure than diazepam patients. Patients who received midazolam had significantly less recall of the overall procedure and the withdrawal of the cystoscope. There were several cases of excessive sedation from the combination of meperidine and a benzodiazepine.

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Study No. 124

Title: A Comparison of Midazolam and Diazepam In Combination With Meperidine During Local Anesthesia for Cystoscopy

Investigator: William R. Fair, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in male patients premedicated with meperidine for cystoscopy.

Subjects

There were 21 males ranging in age from 24 to 78 years. In the midazolam-treated group there were 5 males with a mean age of 68.0 years (range 63-77). In the diazepam group there were 5 males with a mean age of 64.4 years (range 55-78). In the respective placebo groups there were 6 and 5 male patients with mean age of 60.3 years (range 25-76) and 58.8 years (range 30-76).

Study Drugs: See Study No. 125.

Experimental Design

Randomized, double-blind, placebo controlled, parallel study in 21 male patients. The design of this study was similar to that of study 125 since this was a multicenter study following the same protocol.

Results

This study was still in progress at the time of submission and this report details the results of the first 21 patients.

Deviations from Potocol

Three patients were excluded from all efficacy analyses. Patient (midazolam) became unresponsive to painful stimuli and developed a decrease in blood pressure after receiving 0.758 mg/kg of meperidine and 0.152 mg/kg of midazolam. The cystoscopy was cancelled and 1 ml of Narcan was administered to reverse these effects. Patient (placebo, midazolam) and (placebo, diazepam) experienced pain and discomfort during introduction of the cystoscope; consequently, additional medication was required to complete the procedure. Patient received Valium while patient received Innovar.

The first placebo patient received a total of 10 ml of placebo (midazolam) since the cystoscopist did not think the patient was sufficiently sedated. The person administering the placebo did not want to tell the cystoscopist that placebo was being administered; consequently, the total 10 ml was administered.

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The 24 hour questionnaire for patient who received placebo (midazolam), was not included in the analysis since the questionnaire was completed one month after the procedure. Patient who received diazepam, did not complete the 24 hour questionnaire since additional medication was administered postoperatively for another procedure.

The responses to recall of the Trieger Test of one diazepam-treated patient were not included in analysis. This patient could recall doing only one Trieger Test following cystoscopy but did not know whether it was the one or two hour test. One placebo (midazolam) patient did not answer the question of recall of the two hour Trieger Test.

Induction of Intravenous Sedation

There was no significant difference in mean sedation times between active drugs, although midazolam required a shorter time (5 minutes) compared with diazepam (8 minutes) and a smaller dose (0.081 mg/kg vs. 0.129 mg/kg).

Physician's Assessment

There were no significant differences in these assessments between the active drugs with mean assessments ranging from "good" to "excellent." The patients taking placebo ranged from "poor" to "excellent" with the lowest parameter, in general, being quality of sedation.

Patient's Assessment

All recorded responses for the active drugs with respect to quality of sedation were "good to "excellent." All responding midazolam patients and all but one diazepam patient reported that the cystoscopy was not painful and that they would undergo another procedure the same way.

Trieger Test

The psychomotor recovery pattern was similar in both active treatment groups with elevations from baseline values at 1 hour and return to baseline at two hours.

Follow-Up Questionnaire for Amnesia

None of the patients in the active midazolam group and only one in the diazepam group recalled scope introduction and withdrawal.

Safety

Patient, a 65 year old male with a history of chronic obstructive pulmonary disease and arteriosclerotic heart disease became unresponsive to painful stimuli and developed a decrease in blood pressure after receiving 0.759 mg/kg of meperidine and 0.152 mg/kg of midazolam. One milliliter of ilarcan was given. The investigator felt that in view of the patient's age and condition, less drug and slower injection would have prevented the adverse effects.

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Patient experienced burning and stinging during the initial injection of midazolam. The drug was injected more slowly without further complaints. No patient had evidence of venous irritation following the study.

Table 1
Clinical Adverse Experiences

	Number of Patients			
	Midaz- olam	Diaz- epam	Placebo Midaz- olma	Placebo Diaz- epam
<u>Possibly and Probably Related Drug Effects</u>				
<u>Respiratory System</u>				
Respiration Rate Increase	2	3	2	3
Respiration Rate Decrease	1	0	2	1
<u>Cardiovascular System</u>				
Pulse Increase	1	0	0	1
Pulse Decrease	2	0	2	0
MAP Increase	0	1	0	0
MAP Decrease	1	1	0	0
Pain During Injection of Study Drug	1	0	0	0
<u>Central Nervous</u>				
Unresponsive	1	0	0	0

Most changes in vital signs were transient and were not considered clinically significant.

Summary and Conclusions

This study is still in progress and was not analyzed by the sponsor due to the limited number of patients studied at the time of submission. Midazolam patients experienced better sedation and reported less pain associated with the procedure than placebo patients. The midazolam-treated patients reported the quality of sedation as "good" to "excellent" and none recalled introduction and withdrawal of the cystoscope.

A 65 year old midazolam patient with a history of arteriosclerotic heart disease and clinical condition, less drug and slower injection of the drug would have prevented the adverse effects from occurring.

A midazolam patient complained of burning and stinging at the intravenous injection site. When the drug was injected more slowly there were no further complaints. There were no reports of venous irritation following the study. Transient changes in vital signs were observed.

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Study No. 125

Title: A Comparison of Midazolam and Diazepam In Combination With Meperidine During Local Anesthesia for Cystoscopy

Investigator: Guenter Corssen, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in male patients premedicated with meperidine for cystoscopy.

Subjects

There were 41 males ranging in age from 20 to 96 years. In the midazolam-treated group there were 10 males with a mean age of 56.4 years (range 23-96). In the diazepam group there were 11 males with a mean age of 51.6 years (range 20-76). In the respective placebo groups there were 10 males each, with mean age of 51.6 years (range 25-76) and 47.1 years (range 30-76).

Study Drugs:

Patients were randomly divided into four groups: midazolam, diazepam, placebo to match midazolam and placebo to match diazepam. Thirty minutes prior to cystoscopy, all patients received 35-50 mg of meperidine administered intramuscularly followed by the instillation of topical lidocaine jelly into the urethra 5 to 10 minutes before cystoscopy. Patients assigned to midazolam or diazepam treatment groups received 5.0-7.5 mg of the test medication intravenously over a 2-3 minute period. Elderly patients (as identified by the investigator) received 2.50-3.75 mg of the test medications over the same time interval. Incremental doses (25% of initial dose) were administered, if necessary, until the patient's speech became thickened and slurred but the patient was still responsive to verbal commands. Patients assigned to placebo groups received 2-6 ml total volume of solution administered intravenously over a 5 minute period.

Experimental Design

Randomized, double-blind, controlled, parallel group study in patients undergoing diagnostic cystoscopy for the first time. Immediately following cystoscopy, the physician, who did not know which test medication had been administered, evaluated as excellent, good, fair or poor the sedative effects produced by the test medication. The assessments included: (1) patient cooperation, (2) muscle relaxation, (3) ease of cystoscopic examination, (4) quality of sedation, (5) control of bladder spasms, (6) control of pain, (7) control of retching and vomiting, (8) overall tolerance of the procedure. One hour after cystoscopy and one day later in a follow-up questionnaire, patients

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evaluated the sedation during the procedure as excellent, good, fair, poor. On both occasions patients were asked whether they would elect to undergo a future cystoscopy the same way, if necessary. One hour after cystoscopy, patients evaluated the cystoscopic procedure as not painful, somewhat painful or very painful and whether they could recall none, some or all of the procedure. In the follow-up questionnaire patients were also asked whether they could recall clearly, vaguely or not at all events before, during and after cystoscopy.

Recovery from sedation was assessed by the Trieger Test, which was completed by the patient before medication (baseline) and at 60 and 120 minutes following the cystoscopy. Each Trieger Test was evaluated for the number of dots missed and the total deviation (mm) from the dots.

Blood pressure, respiration rate and pulse rate were monitored before, during and after cystoscopy. Changes in vital signs greater than 20% from baseline were identified as possible adverse experiences. The severity of the changes was categorized as:

mild - a change >20 percent but <30 percent from baseline
moderate = a change >30 percent but <50 percent from baseline
severe = a change >50 percent from baseline or treatment required

Clinical adverse experiences were further categorized according to the phase of the study. The phases of the study were defined as follows:

induction = period of test drug administration
maintenance = period of cystoscopy
recovery = post cystoscopy until discharge

Seven to 14 days following the study, the intravenous injection site was examined for tenderness, redness, and induration.

Results

Deviations from Potocol

Two patients who received midazolam were excluded from all efficacy analyses. Patient #5 had a previous history of drug addiction which he did not admit to until after the study. Patient _____ was unable to comprehend all aspects of the study due to senility.

The Trieger Test results for two patients were not included in efficacy analysis. The test results for patient _____ who received placebo (diazepam) were not returned. There was confusion as to what time the Trieger Tests were completed by one midazolam-treated patient _____.

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placebo treatment groups. On the 24 hour questionnaire most patients in all treatment groups could recall the baseline Trieger Test and the Administration of local anesthetic. Most midazolam-treated patients had no recall of the introduction and withdrawal of the cystoscope. When compared to placebo, midazolam treated patients had significantly less recall of the withdrawal of the cystoscope. Most patients who received midazolam placebo could recall both the introduction and withdrawal of the cystoscope. About half of the patients who received diazepam and placebo had no recall of the introduction and withdrawal of the cystoscope. Most patients in all groups could recall the post-treatment Trieger Tests.

Safety

A 96 year old male with Alzheimer's disease experienced excessive sedation following the procedure. This patient received 0.833 mg/kg of meperidine and 0.083 mg/kg of midazolam. The investigator felt that the excessive sedation was probably due to the dosage of meperidine administered.

There were no reports of venous irritation following the study in any of the treatment groups.

Table 1
Clinical Adverse Experiences

	Number of Patients			
	Midaz- olam	Diaz- epam	Placebo Midaz- olam	Placebo Diaz- epam
<u>Possibly and Probably Related Drug Effects</u>				
<u>Respiratory System</u>				
Respiration Rate Increase	1	2	4	2
Respiration Rate Decrease	4	2	0	1
<u>Cardiovascular System</u>				
Pulse Increase	1	2	0	1
Pulse Decrease	0	1	1	0
MAP Increase	1	2	1	0
MAP Decrease	2	1	1	1
<u>Remotely Related Drug Effect</u>				
<u>Miscellaneous</u>				
Excessive Sedation	1	0	0	0

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One midazolam, three diazepam, and one placebo (diazepam) did not return the 24 hour patient questionnaires. Several patients also omitted answering questions on the 24 hour questionnaire,

placebo (midazolam) - recall scope introduction
midazolam - recall two hour Trieger Test
midazolam - recall one and two hour Trieger Test
placebo (diazepam) - recall two hour Trieger Test

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.133 mg/kg of midazolam and 0.187 mg/kg of diazepam. The mean time to reach the sedative end point was comparable between midazolam and diazepam groups.

Physician's Assessment

The physician's assessments were in most instances "good" to "excellent" for midazolam and diazepam treatment groups, while assessments of sedation for patients in the placebo groups, with the exception of patient cooperation, and control of retching and vomiting, were "poor" to "fair." These latter two parameters were rated as "excellent" or "good" in all 4 groups. Both active treatment groups were evaluated significantly better than their respective placebo groups except as noted above.

Patient's Assessment

There were no significant differences between actual treatment groups or between diazepam and placebo on rating the quality of sedation or willingness to undergo the procedure the same way again. On the two test occasions, one hour after the procedure and on the following day, midazolam treated patients evaluated sedation significantly better than placebo patients. On the following day significantly more midazolam patients were willing to undergo the procedure the same way. There were no significant differences among the treatment groups for pain associated with the cystoscopy.

Trieger Test

On both the one and two hour post-treatment Trieger Tests, midazolam-treated patients had a significantly increased number of dots missed and deviations from the dots compared with patients who received placebo. Patients in the midazolam, diazepam and diazepam placebo groups all missed more dots on the one and two hour post treatment Trieger Tests than at baseline.

Follow-Up Questionnaire for Amnesia

One hour after cystoscopy midazolam and diazepam treatment groups had significantly less recall of the procedure when compared with their respective

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Most changes in vital signs were transient and were not considered clinically significant. Changes in vital signs were usually mild to moderate with very few classified as severe. A severe increase in pulse rate during cystoscopy was observed in one diazepam treated patient. Severe decreases in respiration rate during cystoscopy were also observed in one midazolam patient and one diazepam patient.

Summary and Conclusions

This randomized, double-blind study compared the use of IV midazolam with IV diazepam and placebo to provide sedation during cystoscopy. As adjuncts to topical anesthesia and intramuscular meperidine both midazolam and diazepam were effective sedative agents. The physician's assessments were in most cases "good" to "excellent" for both active treatment groups while assessments of most sedation parameters in the placebo groups were "fair" to "poor." The active treatment groups were evaluated significantly better than their corresponding placebo groups on all of the physician's assessments, except for control of retching and vomiting and patient cooperation which were rated as "good" or "excellent" in all 4 groups.

Midazolam patients rated quality of sedation significantly better than the placebo, as well as having significantly more patients willing to undergo a future procedure the same way and significantly less patients had recall of the overall procedure and the withdrawal of the cystoscope. There were no significant differences between active treatment and placebo on the patient's assessments of the procedure. One hour after the procedure, diazepam patients had significantly less recall of the procedure than did the corresponding placebo-treated patients.

With respect to psychomotor recovery, the midazolam-treated patients showed a significantly greater number of dots missed and deviation from the dots on the post-treatment Trieger Tests when compared with placebo.

Transient fluctuations in vital signs were observed in all treatment groups but were not considered clinically significant. A 96 year old midazolam patient developed excessive sedation following the procedure but this was felt by the investigator to be related to the dose of meperidine. There was no venous irritation.

This study showed that midazolam, when used in combination with meperidine and a local anesthetic agent, is as safe and effective as diazepam in inducing sedation intravenously for cystoscopy.

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Study No. 127

Title: A Comparison of Midazolam and Diazepam In Combination With Meperidine During Local Anesthesia for Cystoscopy

Investigator: Philip H. Hanno, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in adult males premedicated with meperidine for cystoscopy.

Experimental Design

Randomized, double-blind, placebo and reference drug controlled study in patients undergoing diagnostic cystoscopy for the first time.

Subjects

There were 14 males ranging in age from 55 to 76 years. In the midazolam-treated group there were 4 males with a mean age of 66.5 years (range 60-76). In the diazepam group there were 3 males with a mean age of 59.0 years (range 58-60).

In the respective placebo groups there were 3 and 4 males with mean ages of 62.0 years (range 57-69) and 60.5 years (range 55-70).

Study Drugs: See Study 125.

Results

Fourteen of forty patients were recruited into the study by the time of submission.

Deviations from Protocol

Two patients in each placebo group were excluded from efficacy analyses because each required 10 mg of diazepam to complete the procedure because of pain and discomfort experienced during introduction of the cystoscope.

Induction of Intravenous Sedation

Comparable levels of sedation were achieved during similar time intervals with mean doses of 0.089 mg/kg of midazolam and 0.145 mg/kg of diazepam.

Physician's Assessment

Similar assessments for all parameters were made for both active treatment groups.

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Patient's Assessment

Similar assessments were made for both active treatment groups.

Trieger Test

Patterns of psychomotor recovery were dissimilar for both active treatment groups with maximum elevations from baseline in number of dots missed and total deviation from dots at one hour with return to baseline for the midazolam group and maximum elevations from baseline at two hours in the diazepam group.

Follow-Up Questionnaire for Amnesia

No patients in the midazolam group recalled scope introduction and withdrawal on the following day, although 1 recalled cystoscopy one hour after the procedure.

Safety

The only adverse experiences observed were mild increases in mean arterial pressure and pulse rate during cystoscopy. No changes in vital signs were observed during induction of sedation or recovery. All changes in vital signs were transient and were not considered clinically significant. No patient had evidence of irritation at the intravenous site following the study.

Summary and Conclusions

The sponsor did not undertake a statistical analysis of the study due to the limited number of patients studied (14 of 40) at the time of submission. Transient fluctuations in blood pressure and pulse rate were observed but were not considered clinically significant. There was no venous irritation.

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Study No. 128

Title: A Comparison of Midazolam and Diazepam Administered Intravenously With Local Anesthesia for Cystoscopy

Investigator: Russell Lawson, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in adult males premedicated with meperidine for cystoscopy.

Experimental Design

Randomized, double-blind, placebo and reference drug controlled study in patients undergoing diagnostic cystoscopy for the first time.

Subjects

There were 19 males ranging in age from 18 to 82 years. In the midazolam group there were 5 males with a mean age of 54.0 years (range 18-82). In the diazepam group there were 4 males with a mean age of 68.0 years (range 62-78). In the respective placebo groups there were 5 males each with mean ages of 65.4 years (range 53-82) and 55.0 years (range 24-73).

Study Drugs: See Study 125.

Results

Nineteen of forty patients were recruited into the study by the time of submission.

Deviations from Protocol

One patient who received placebo (diazepam) was excluded from the efficacy evaluation for receiving an excludable concomitant medication (Ativan) within 24 hours of the procedure.

The Trieger Test results of two are not included. Patient _____, who received placebo (midazolam), did not understand the directions for completing the test. Patient _____ who received diazepam, had Parkinson's disease.

Induction of Intravenous Sedation

Comparable levels of sedation were obtained with mean doses of 0.089 mg/kg midazolam and 0.052 mg/kg diazepam. The active treatment groups reached the sedative end point in comparable mean times (3.0 minutes, midazolam, 2.6 minutes diazepam).

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Physician's Assessment

Similar "good" to "excellent" results were produced in both active treatment groups.

Patient's Assessment

"Good" to "excellent" ratings were achieved for both active drug groups one hour after the procedure and on the following day. All patients in both active treatment groups said they would elect to undergo a future procedure the same way. All midazolam patients said there was no pain associated with the cystoscopy, whereas, 3 of 4 diazepam patients noted some pain during the procedure.

Trieger Test

The two active treatment groups showed similar patterns of psychomotor recovery, with elevations from the baseline in number of dots missed and total deviation from the dots at 1 hour and return toward baseline at two hours.

Follow-Up Questionnaire for Amnesia

There was no recall of scope introduction and withdrawal in either active treatment group.

Safety

An 81 year old patient who received 1.14 mg/kg of meperidine and 0.057 mg/kg of midazolam developed excessive sedation during the cystoscopy. No corrective measures were required. Patient who received midazolam, developed tenderness, redness and induration at the intravenous injection site for 2 days following the study.

A 78 year old patient with a history of cerebral vascular disease, experienced excessive sedation after receiving 0.77 mg/kg of meperidine. Because of this the patient received only 0.2 ml (0.016 mg/kg) of diazepam.

Patient who received placebo (midazolam) experienced dry mouth which was attributed to meperidine. Patient who also received placebo (midazolam), experienced tenderness for one day following the study.

A placebo (diazepam) treated patient with a history of arteriosclerotic vascular disease, experienced dizziness upon arising from bed one hour after the cystoscopy. His blood pressure, which was 126/67 mmHg before cystoscopy, increased to 181/108 mmHg during the procedure and decreased to 88/68 mmHg one hour after cystoscopy.

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Table 1
Clinical Adverse Experiences

	Number of Patients			
	Midaz- olam	Diaz- epam	Placebo Midaz- olma	Placebo Diaz- epam
<u>Possibly and Probably Related Drug Effects</u>				
<u>Respiratory System</u>				
Respiration Rate Increase	3	3	3	3
Respiration Rate Decrease	2	1	3	3
<u>Cardiovascular System</u>				
Pulse Increase	2	0	0	0
Pulse Decrease	1	0	2	2
MAP Increase	0	0	1	2
MAP Decrease	2	1	0	1
Tenderness of Vein	1	0	1	0
Redness of Vein	1	0	0	0
Induration of Vein	1	0	0	0
<u>Gastrointestinal</u>				
Dry Mouth	0	0	1	0
<u>Spinal Senses</u>				
Dizziness	0	0	0	1
<u>Miscellaneous</u>				
Excessive Sedation	1	0	0	0
<u>Remotely Related Drug Effect</u>				
<u>Miscellaneous</u>				
Excessive Sedation	0	1	0	0

Most changes in vital signs were classified as mild or moderate. Several patients in various treatment groups had severe changes in vital sign measurements but these changes were not considered to be clinically significant.

Summary and Conclusions

A statistical analysis of this study was not undertaken due to the limited number of patients studied (19 of 40) by the time of submission. One elderly midazolam patient and one elderly diazepam patient experienced excessive

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sedation probably related to too high a dose of meperidine premedication. One placebo (diazepam) patient experienced dizziness upon arising, related to hypotension, one hour following cystoscopy. Following the study venous irritation was observed in one placebo (midazolam) and one midazolam-treated patient. Transient fluctuations in vital signs were observed but were not considered clinically significant.

Pooled Study Summary

Study Nos. 101, 110, 120, Protocol 2238A

Title: A Comparison of Midazolam and Diazepam Administered Intravenously With Local Anesthesia for Gastroscopy

Subjects

One hundred nine patients (ASA I or II) undergoing diagnostic gastroscopy for the first time participated in the study. The study population consisted of 29 non-pregnant females and 80 males ranging in age from 19 to 74 years. In the midazolam group there were 54 patients comprised of 39 males and 15 females with a mean age of 49.1 years (range 19-73). In the diazepam group there were 55 patients comprised of 41 males and 14 females with a mean age of 47.4 years (range 23-74).

Results

Differences Among Study Centers

Dr. Isenberg's study (#120) was not included in efficacy analyses because the drug shipment was divided incorrectly between two study sites. This resulted in compromised randomization since drug codes were not assigned in date order. The study was included in the pooled safety analyses.

There were differences between centers in the dose of midazolam or diazepam required for induction of sedation. Patient's in Dr. Lanza's study (#101) required approximately twice as much midazolam to reach the sedative end point as did patients in the other two studies.

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.164 mg/kg of midazolam and 0.264 mg/kg of diazepam. Midazolam-treated patients required a significantly shorter mean time to reach the sedative end point of slurred speech than did diazepam patients (2.8 vs. 4.8 minutes).

Physician's Assessment

The physician's assessment of sedation was the same for both test medications except that diazepam-treated patients experienced significantly better muscle relaxation and were more cooperative.

Patient's Assessment

These were comparable between test groups, except patients who received midazolam reported significantly less pain associated with the gastroscopy.

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Trieger Test

Recovery from sedation as measured by this test was comparable between treatment groups.

Follow-Up Questionnaire for Amnesia

Following test drug administration, midazolam-treated patients had significantly less recall of the introduction and withdrawal of the gastroscope. There were also significantly more midazolam patients with diminished recall of the one and two hour post-treatment Trieger Tests.

Safety

Four midazolam and 7 diazepam-treated patients had evidence of irritation at the intravenous injection site at the follow-up examination. There were several reports of drowsiness, dizziness, weakness and lethargy in each group, but they were associated with the high doses of test drug received by patients at one study center. There were no clinically significant changes in vital signs.

Summary and Conclusions

In this multicenter study midazolam was demonstrated to be as safe and effective as diazepam in inducing sedation for gastroscopy when administered as an adjunct to topical anesthesia. Patients who received midazolam were more relaxed, had less pain and had diminished recall of the procedure.

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Study No. 101

Title: A comparison of Midazolam and Diazepam Administered Intravenously With Local Anesthesia for Gastroscopy

Investigator: Frank L. Lanza, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in patients undergoing gastroscopy for the first time.

Experimental Design

Randomized, double-blind parallel study in 27 patients. The design of this study was similar to that of study 110 since this was a multicenter study following the same protocol.

Subjects

There were 19 non-pregnant females and 8 males ranging in age from 23 to 67 years. In the midazolam group there were 4 males and 10 females with a mean age of 40.2 years (range 23-62). In the diazepam group there were 4 males and 9 females with a mean age of 44.1 years (range 48-140).

Study Drugs: See Study 110.

Results

Deviations from Protocol

One diazepam-treated patient did not return the 24 hour patient questionnaire. Patient (diazepam) did not evaluate quality of sedation on the 24 hour questionnaire. Midazolam patient did not complete the two hour post-treatment Trieger Test.

Induction of Intravenous Sedation

Comparable levels of sedation were obtained with mean doses of 0.225 mg/kg midazolam and 0.366 mg/kg diazepam. Midazolam-treated patients reached the sedative end point almost twice as fast as the diazepam group (mean 3.13 vs. 6.08); the difference was statistically significant for gastroscopies of similar duration.

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Physician's Assessment

There were no statistically significant differences between treatments in the physician's assessment of sedation. The assessment was "fair" to "good" for both groups in most instances.

Patient's Assessment

All patients in both test groups rated sedation as "good" or "excellent" on both rating periods. Both test groups had little or no pain associated with the gastroscopy and most patients were willing to undergo the procedure the same way again.

Trieger Test

One hour following the procedure, midazolam patients had a significantly greater number of dots missed and total deviation from the dots compared with the diazepam group. At two hours the results were similar.

Follow-up Questionnaire for Amnesia

All patients in both groups recalled the events prior to administration of the test drug. No patient in either group recalled the introduction and withdrawal of the scope. The midazolam patients also had significantly less recall of the one and two hour post treatment Trieger Tests.

Safety

Patient _____ who received 0.217 mg/kg of midazolam, was lethargic, weak and dizzy for several hours following the study. The patient had a history of hypoglycemia and hypothyroidism.

One diazepam patient _____ developed weakness after the study. This patient who was on chronic diazepam therapy for anxiety, required 0.738 mg/kg of diazepam to sedate. Technically this case does not represent a protocol violation since, according to the case record, diazepam was discontinued 2 days prior to the procedure. It would have been prudent if the investigator had excluded the subject, who was taking diazepam 2.5 mg t.i.d. on a chronic basis. Patient _____ who also received diazepam, had a headache and felt nauseated the evening following the procedure, while another diazepam-treated patient _____ was lethargic following the gastroscopy.

Two midazolam patients _____ (.203 mg/kg and .206 mg/kg) and one diazepam patient _____ experienced drowsiness following the study, which may well have been related to the high doses of test drugs which were administered to the patients in this study.

One patient in each treatment group (_____ - midazolam and _____ - diazepam) showed evidence of venous irritation following the study.

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Table 1
Clinical Adverse Experiences

	<u>Midazolam</u>		<u>Diazepam</u>	
	<u># pts.</u>	<u>Percent</u>	<u># pts.</u>	<u>Percent</u>
<u>Possibly and Probably Related Drug Effects</u>				
<u>Respiratory System</u>				
Respiration Rate Increase	3	57.1	4	30.8
Respiration Rate Decrease	1	7.1	2	15.4
<u>Cardiovascular System</u>				
Pulse Increase	5	35.7	6	46.2
Pulse Decrease	1	7.1	1	7.7
MAP Increase	2	14.3	2	15.4
Tenderness of Vein	1	7.1	0	0
Induration of Vein	0	0	1	7.7
<u>Gastrointestinal</u>				
Nausea	0	0	1	7.7
<u>Central Nervous</u>				
Headache	0	0	1	7.7
<u>Special Sense</u>				
Dizziness	1	7.1	0	0
<u>Miscellaneous</u>				
Apathy	0	0	1	7.7
Drowsy	2	14.3	1	7.7
Lethargy	1	7.1	0	0
Weak	1	7.1	1	7.7
<u>Remotely Related Drug Effect</u>				
<u>Gastrointestinal</u>				
Throat-Pain	0	0	1	7.7

Most changes in vital signs were transient and were most often associated with the gastroscopy. Changes were usually mild or moderate with very few classified as severe. Severe increases in respiration and pulse rate were observed in several patients in both treatment groups.

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Summary and Conclusions

This randomized, double-blind study compared the use of IV midazolam with IV diazepam to provide sedation during gastroscopy. The study, at the time of submission, was still in progress, and this submission represents an interim report of the first 27 patients. As adjuncts to local anesthesia, both drugs were effective intravenous sedative agents for gastroscopy. Physician's assessments of sedation were "fair" to "good" in most instances. All patients rated sedation "good" or "excellent" and reported little or no pain associated with the procedure.

Failure to recall the introduction and withdrawal of the gastroscope was induced in all patients. This was extended out for 2 hours with respect to recall of the post-treatment Trieger Tests by 64% of the midazolam-treated patients. On the one hour Trieger Test midazolam patients had a significantly higher increase in number of dots missed and total deviation from the dots, compared with the diazepam-treated patients. By two hours these results had returned to near the baseline value.

One patient in each treatment group had signs of venous irritation following the study. Transient fluctuations were observed in both treatment groups but were not considered clinically significant. One diazepam patient had a headache and felt nauseated following the procedure.

Several patients in each group experienced weakness, drowsiness or lethargy following the study. These side effects were probably related to the relatively high doses of both study drugs administered in this study.

This study showed that midazolam, when used in combination with a local anesthetic agent, is as safe and effective as diazepam in inducing sedation for gastroscopy. Patients who received midazolam had no recall of the introduction and withdrawal of the gastroscope and many had impaired recall of the post-treatment Trieger Tests.

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Study No. 110

Title: A comparison of Midazolam and Diazepam Administered Intravenously With Local Anesthesia for Gastroscopy

Investigator: George Dewey Dunn, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in patients undergoing gastroscopy for the first time.

Experimental Design

Randomized, double-blind parallel study in 41 adults undergoing gastroscopy. Prior to gastroscopy, midazolam or diazepam was administered by random coded assignment. Immediately following the gastroscopy, the physician evaluated as excellent, good, fair or poor the sedative effects produced by the test medication. The assessments included (1) patient cooperation, (2) muscle relaxation, (3) ease of gastroscopic examination, (4) control of gag reflex, (5) control of laryngospasm, (6) control of cough reflex, (7) control of retching and vomiting, (8) control of salivation and (9) overall tolerance of the procedure. One hour after gastroscopy and one day later in a follow up questionnaire, patients evaluated the sedative during the procedure as excellent, good, fair or poor. On both occasions patients were asked whether they would elect to undergo a future gastroscopy the same way. One hour after the procedure, patients evaluated the procedure as not painful, somewhat painful or very painful and whether they could recall none, some or all of the gastroscopy. In the follow-up questionnaire, patients were asked about their level of recall of events before, during and after gastroscopy.

Recovery from sedation was assessed by the Trieger Test which was administered before medication (baseline) and at 60 and 120 minutes after the procedure. Each test was evaluated for the number of dots missed and the total deviation (mm) from the dots.

Vital signs were monitored before, during and after gastroscopy. Changes greater than 20% from baseline were identified as possible adverse experiences, and were categorized according to the phase of the study as induction, maintenance or recovery. Seven to 14 days following the study, the intravenous injection site was examined for tenderness, redness and induration.

Subjects

There was 1 non-pregnant female and 40 males ranging in age from 27 to 70 years (ASA status I or II). In the midazolam group there were 19 males and 1 female with a mean age of 51.8 years (range 27-67). In the diazepam group there were 21 males with a mean age of 48.7 (range 30-70).

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Study Drugs

Approximately 30 minutes before the gastroscopy, atropine 0.5 mg was administered intramuscularly. Following topical anesthetic administration, 10-15 mg of either midazolam or diazepam was administered intravenously over a 2-3 minutes period. Elderly patients (as identified by the investigator) received 5.0 - 7.4 mg of the test medications over the same time interval. Incremental doses (25% of initial dose) were administered, if necessary, until the patients speech became slurred.

Results

Deviations from Protocol

The physician's assessment of the procedure and the one hour-patient questionnaire were not obtained for patient of the diazepam group. Patient of the midazolam group was unable to complete the Trieger Tests due to poor vision.

Induction of Intravenous Sedation

Comparable levels of sedation were obtained with mean doses of 0.103 mg/kg of midazolam and 0.161 mg/kg of diazepam. The average time to reach the sedative end point was 2.39 and 3.56 minutes for midazolam and diazepam, respectively, with similar duration of procedures.

Physician's Assessment

The physician's assessment of sedation was "good" to "excellent" for both groups of patients. There were no statistically significant differences between treatments.

Patient's Assessment

After the procedure and the following day all midazolam and 95% of the diazepam patients rated the sedation "good" or "excellent." Significantly more diazepam-treated patients found the gastroscopy "somewhat painful." All patients indicated one hour after the procedure that they would have a future gastroscopy done the same way; and, on the following day, all midazolam and 95% of the diazepam patients responded affirmatively.

Trieger Test

There were no significant differences between groups in recovery from sedation. There was an increase in number of dots missed and total deviation from the dots compared with the baseline in both groups one hour after the gastroscopy with a trend toward return to baseline at two hours.

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Follow-Up Questionnaire for Amnesia

Most patients could recall events prior to test drug administration. Significantly more midazolam-treated patients had no recall of the introductions and withdrawal of the gastroscope and of the one hour Trieger Test. Recall of the two hour Trieger Test was not significantly different between groups and was present in most of the patients.

Safety

On the day following the procedure, patient (diazepam) developed conjunctivitis and on day three there was a rash on both legs and a swelling of the left axilla.

Patient (midazolam) experienced severe chest pain due to a dilated esophagus. This patient also was drowsy following the procedure. One midazolam patient and two diazepam patients experienced mild headaches following the procedure. Patient - diazepam was dizzy following the procedure.

Two midazolam-treated patients had venous irritation on the follow-up examination. Four diazepam-treated patients also had venous irritation.

Most changes in vital signs were transient and were most often associated with the gastroscopy. One change was observed during induction in which one diazepam patient had a mild increase in pulse rate. Most changes were mild to moderate.

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Table 1

Clinical Adverse Experiences

	<u>Midazolam</u>		<u>Diazepam</u>	
	<u># pts.</u>	<u>Percent</u>	<u># pts.</u>	<u>Percent</u>
<u>Probably and Possibly Related Drug Effects</u>				
<u>Respiratory System</u>				
Respiration Rate Increase	3	15.0	6	28.6
Respiration Rate Decrease	5	25.0	3	14.3
<u>Cardiovascular System</u>				
Pulse Increase	10	50.0	6	28.6
Pulse Decrease	0	0	3	14.3
MAP Increase	3	15.0	8	38.1
MAP Decrease	5	25.0	5	23.8
Tenderness of Vein	0	0	2	9.5
Redness of Vein	1	5.0	1	4.8
Induration of Vein	1	5.0	2	9.5
<u>Integumentary</u>				
Rash on legs	0	0	1	4.8
Swollen armpit	0	0	1	4.8
<u>Special Sense</u>				
Conjunctivitis	0	0	1	4.8
Dizziness	0	0	1	4.8
<u>Central Nervous</u>				
Headache	1	5.0	1	4.8
<u>Miscellaneous</u>				
Drowsy	1	5.0	0	0
<u>Remotely Related Drug Effect</u>				
<u>Respiratory System</u>				
Sore throat	1	5.0	0	0
<u>Gastrointestinal</u>				
Dry mouth	1	5.0	0	0
<u>Central Nervous</u>				
Headache	0	0	1	4.8
<u>Miscellaneous</u>				
Chest pain	1	5.0	1	4.8

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Summary and Conclusions

This randomized double-blind study compared the use of IV midazolam with IV diazepam to provide sedation during gastroscopy. As adjuncts to topical anesthesia, both agents were effective sedative agents. Assessments of sedation were "good" to "excellent" for both test medications. Significantly more diazepam patients found the gastroscopy "somewhat painful." One hour following the procedure all patients indicated that they would undergo the gastroscopy the same way again, and these responses were nearly duplicated on the following day.

There were no significant differences between treatments on the Trieger Test; however, both groups showed some impairment of performance one hour after the procedure with return toward baseline at two hours. Midazolam-treated patients had significantly less recall of the introduction and recall of the gastroscope as well as the one hour post-treatment Trieger Test.

One patient who received diazepam developed conjunctivitis, a rash on both legs, and swelling of the left axilla. One midazolam and two diazepam patients had mild headaches following the gastroscopy. Two midazolam and four diazepam patients had venous irritation at the injection site following the study. Transient fluctuations in vital signs were observed in both treatment groups but were not considered clinically significant.

This study showed that midazolam, when used in combination with a local anesthetic agent, is as safe and effective as diazepam in inducing sedation intravenously for gastroscopy. Midazolam was more effective in inducing diminished recall of the procedure.

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Study No. 120

Title: A comparison of Midazolam and Diazepam Administered Intravenously With Local Anesthesia for Gastroscopy

Investigator: Jon I. Isenberg, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in patients undergoing gastroscopy for the first time.

Experimental Design

Randomized, double-blind parallel study in 41 adults. The design of this study was similar to that of study 110 since this was a multicenter study following the same protocol.

Subjects

There were 9 non-pregnant females and 32 males ranging in age from 19 to 74 years (ASA status I or II). In the midazolam group there were 16 males and 4 females with a mean age of 52.7 (range 19-73). In the diazepam group there were 16 males and 5 females with a mean age of 48.2 years (range 25-74).

Study Drugs: See Study 110.

Results

Deviations from Protocol

Midazolam patient _____ was excluded from all efficacy analyses since the patient received an excluded concomitant medication (thioridazine) on the day of the study. This patient was included in all analyses of safety.

One midazolam patient _____ refused to stay for the two hour Trieger Test. No weight was recorded for patient _____ who received 4.5 mg of midazolam.

Several patients omitted answering a question on the 24 hour questionnaire.

- #1 (Midazolam) - Quality of sedation
- #1 (Midazolam) - Future procedure done same way
- #13 (Diazepam) - Recall withdrawal of gastroscop
- #33 (Midazolam) - Recall withdrawal of gastroscop
- #35 (Diazepam) - Future procedure done same way
- #46 (Diazepam) - Quality of sedation

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Induction of Intravenous Sedation

Comparable levels of sedation were obtained with mean doses of 0.117 mg/kg of midazolam and 0.198 mg/kg of diazepam. One midazolam patient required an additional dose of 0.063 mg/kg to maintain sedation. Midazolam-treated patients required a significantly shorter time to reach the sedative end point (3.2 vs. 5.9 minutes), with similar average duration of gastroscopies.

Physician's Assessment

The physician's assessments of sedation were in most instances "fair" to "excellent" for both treatment groups. There were no significant intergroup differences in the assessment.

Patient's Assessment

The majority of patients rated the sedation produced by either drug as "good" or "excellent." Both groups reported little or no pain associated with the gastroscopy. Most patients were willing to undergo the procedure the same way again.

Trieger Test

There were no significant differences between treatment groups in recovery from sedation. Both groups showed a slight increase in number of dots missed and total deviation from the dots one hour after the gastroscopy. By two hours, the results had returned to near the baseline values.

Follow-Up Questionnaire for Amnesia

Most patients in both groups recalled the events which preceded test drug administration. Although there was no significant difference between groups in recall of the procedure one hour later, on the following day, significantly less midazolam-treated patients had recall of the introduction and withdrawal of the gastroscope than those who received diazepam. The majority of the patients in both groups recalled both post-treatment Trieger Tests.

Safety

Patient who received 0.157 mg/kg of midazolam was argumentative during the gastroscopy; therefore, an additional 5 mg was administered to calm the patient. Induration of the intravenous injection site was also observed in this patient for one week following the study.

Several days following the study, one diazepam patient developed tinnitus which lasted for 3 days. Another diazepam patient had a supraorbital headache for one week following the study. These reactions were considered to be remotely related to the administration of diazepam.

Two diazepam patients had evidence of venous irritation following the study.

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Table 1

Clinical Adverse Experiences

	<u>Midazolam</u>		<u>Diazepam</u>	
	<u># pts.</u>	<u>Percent</u>	<u># pts.</u>	<u>Percent</u>
<u>Possibly and Probably Related Drug Effects</u>				
<u>Cardiovascular System</u>				
Pulse Increase	7	35.0	14	66.7
Pulse Decrease	3	15.0	4	19.0
MAP Increase	4	20.0	2	9.5
MAP Decrease	4	20.0	2	9.5
Tenderness of Vein	0	0	2	9.5
Induration of Vein	1	5.0	1	4.8
<u>Integumentary</u>				
Inflammation at injection site	0	0	1	4.8
<u>Miscellaneous</u>				
Argumentative	1	5.0	0	0
<u>Remotely Related Drug Effect</u>				
<u>Central Nervous</u>				
Headache	0	0	1	4.8
<u>Special Sense</u>				
Tinnitus	0	0	1	4.8

Most changes in vital signs were transient and were not considered clinically significant. One midazolam-treated patient had a severe increase in mean arterial pressure during the gastroscopy. A severe increase in pulse rate was observed in several patients in both groups during gastroscopy and recovery.

Summary and Conclusions

This randomized, double-blind study compared the use of IV midazolam with IV diazepam to provide sedation during gastroscopy. As adjuncts to topical anesthesia, both agents were effective sedative agents. Assessments of sedation by the physician were "fair" to "excellent" in most instances. Most patients rated the quality of sedation as "good" or "excellent" and both groups reported little or no pain associated with the gastroscopy. Most patients were willing to undergo a future gastroscopy the same way again.

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Most patients recalled events prior to gastroscopy. While there was no difference between groups one hour after the procedure, significantly more midazolam patients had no recall of the gastroscope introduction and withdrawal on the following day. Most patients had recall of all the Trieger Tests. Recovery from sedation as assessed by the Trieger Tests was comparable between groups.

One midazolam patient became argumentative during the procedure and an additional dose of the drug was given. Induration of the intravenous site was also seen in this patient.

With respect to diazepam-treated patients, one complained of tinnitus for several days while another had a supraorbital headache lasting for a week. These were considered remotely related to the treatment. Two patients had venous irritation at the injection site. Transient changes in vital signs were observed in both groups but were not considered clinically significant.

This study showed that midazolam, when used in combination with a local anesthetic agent, is as safe and effective as diazepam in inducing sedation for gastroscopy. Midazolam was more effective in inducing diminished recall of the procedure.

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Pooled Study Summary

Study Nos. 102, 104, Protocol 2239A

Title: A Comparison of Midazolam and Diazepam in Combination With Meperidine During Local Anesthesia for Gastroscopy

Subjects

Forty-one patients (ASA Status I or II) undergoing coronary angiography were the subjects of this study. The study population was comprised of 15 non-pregnant females and 26 males ranging in age from 20 to 76 years. In the midazolam group there were 21 subjects comprised of 10 males and 11 females with a mean age of 50.5 years (range 20-76). In the diazepam group there were 20 subjects comprised of 16 males and 4 females with a mean age of 51.7 years (range 21-73).

Results

Differences Between the Centers

The protocol specified that all patients were to receive 50 mg of meperidine with this dose adjusted when necessary to match special requirements of the patients (age, weight, debility). Dr. White administered meperidine at a dose of 1 mg/kg to all patients in his study without considering the patient's age or condition. Several patients in his study experienced extended periods of drowsiness (up to 100 minutes) following the completion of the study. This was believed to be related to the combined effects of a 1 mg/kg dose of meperidine administered concomitantly with midazolam or diazepam.

Induction of Intravenous Sedation

Comparable levels of intravenous sedation were attained with mean doses of 0.095 mg/kg of midazolam and 0.180 mg/kg of diazepam. Two patients in Dr. White's study (one in each treatment group) required maintenance sedation doses for completion of the procedure.

Midazolam patients required a significantly shorter mean time (4.3 minutes) to reach the sedative end point than did diazepam patients (6.1 minutes).

Physician's Assessment

In most instances the physicians' assessments of the sedative properties of the test drugs were "good" to "excellent". Diazepam-treated patients had significantly better control of retching and vomiting.

000104

Patient's Assessment

On both rating occasions (1 hour after the procedure and the following day) all diazepam and 95% of midazolam-treated patients rated sedation as "good" or "excellent". Most patients in both treatment groups reported little or no pain associated with the gastroscopy, although 5% of the midazolam group reported the procedure as "very painful". All the diazepam and 95% of the midazolam group were willing to have a future procedure done the same way again.

Trieger Test

There were increases in number of dots missed and deviations from the dots in both treatment groups one hour following the procedure. At two hours these values had returned toward the baseline values.

Follow-Up Questionnaire for Amnesia

Most patients in both groups could recall all events which occurred prior to test drug administration. Following test drug administration the majority of patients in both groups had diminished recall of the procedure. A significantly larger number of midazolam patients had diminished recall of the one hour Trieger Test than in the diazepam group.

Safety

A remotely related to midazolam myocardial infarction was detected in one male patient on follow-up examination. One midazolam patient experienced hypotension at the end of the procedure which was reversed by Narcan, and was attributed to the administration of meperidine.

Three midazolam and two diazepam patients had evidence of venous irritation following the study.

Five patients in Dr. White's study (#102), two who received midazolam and three who received diazepam experienced an extended period of drowsiness following the completion of the study. This may have been related to excessive meperidine in individual cases combined with midazolam or diazepam.

Comparable changes in vital signs were observed in all phases of the study.

Summary and Conclusions

In this multicenter study midazolam was used to provide sedation during gastroscopy. It was compared to diazepam when administered intravenously as an adjunct to meperidine, atropine and a topical anesthetic agent.

000103

Comparable levels of sedation were attained with mean doses of 0.095 mg/kg of midazolam and 0.180 mg/kg of diazepam. Midazolam patients required a significantly shorter mean time to reach the sedative end point of slurred speech than did diazepam-treated patients (4.3 vs. 6.1 minutes).

The sedative and impairment of recall properties of midazolam and diazepam were similar as rated by the physicians and the patients. In both assessments the sedative properties were rated "good" or "excellent". Both drugs produced impairment recall of the procedure. Psychomotor recovery was similar for the two groups.

Transient comparable fluctuations in vital signs occurred in both groups. Hypotension noted in one midazolam-treated patient was attributed to meperidine. Several patients in one study had prolonged drowsiness and this occurred in both drug groups. This effect was attributed to the combined effects of 1 mg/kg of meperidine administered concomitantly with the sedative agent.

The results of this study showed that midazolam, when used with meperidine and a topical anesthetic agent, is as safe and effective as diazepam in inducing sedation and producing diminished recall of the procedure. Doses of both meperidine and the benzodiazepines should have been reduced to prevent oversedation of some patients.

000108

Study No. 102

Title: A Comparison of Midazolam and Diazepam in Combination With Meperidine During Local Anesthesia for Gastroscopy

Investigator: Paul F. White, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in 21 adults undergoing gastroscopy for the first time.

Subjects

Twenty-one patients (ASA I or II) undergoing diagnostic gastroscopy for the first time. The study population was comprised of 5 non-pregnant females and 16 males ranging in age from 22 to 73 years. In the midazolam group there were 8 males and 3 females with a mean age of 55.3 years (range 22-69). In the diazepam group there were 8 males and 2 females with a mean age of 56.9 years (range 28-73).

Study Drugs: See Study 104

Experimental Design: See Study 104

Results

Deviations from Protocol

Two patients in the midazolam group were excluded from all efficacy analyses. Patient _____ was excluded because morphine, which was an excludable concomitant medication, was administered prior to the procedure to alleviate severe abdominal pain resulting from a pancreatic pseudocyst. Patient _____ required the administration of a narcotic antagonist to reverse meperidine-induced hypotension.

Induction of Intravenous Sedation

Comparable levels of intravenous sedation were achieved with mean doses of 0.091 mg/kg of midazolam and 0.187 mg/kg diazepam. An additional dose to maintain sedation was required by one patient in each treatment group _____. The mean time to reach the sedative end point and the duration of the procedures were similar for both groups.

000107

Physician's Assessment

The physician's assessment of sedation was in most instances "good" to "excellent" for both midazolam and diazepam-treated patients. There were no significant differences between treatments in the physician's assessment of sedation.

Patient's Assessment

One hour after the procedure all but one midazolam patient rated the sedation produced by each drug as "good" or "excellent" and reported little or no pain associated with the gastroscopy. On the following day, one midazolam patient rated sedation as fair and also felt that the gastroscopy was very painful. All patients indicated, one hour after the procedure, that they would elect to undergo the procedure the same way again. On the following day, one midazolam patient changed his response.

Trieger Test

There were no significant differences between the two groups in psychomotor recovery from sedation. There was an increase in the number of dots missed and total deviation from the dots compared with the baseline in both groups one hour after the procedure with return toward the baseline values at two hours.

Follow-Up Questionnaire for Amnesia

Most patients could recall events prior to sedative administration. Failure of recall of scope introduction and withdrawal was induced in all but 1 midazolam and in 2 diazepam patients at one hour after the procedure and in all but 3 midazolam and 1 diazepam patients on the following day.

Safety

On returning 11 days after gastroscopy for the follow-up examination, a 69 year-old male patient (midazolam) with a previous history of myocardial infarction, reported experiencing severe chest pains for several weeks. An electrocardiogram revealed an anterior myocardial infarction of undetermined age. The investigator felt that this event was remotely related to the test drug.

A 66 year-old male, who received 0.100 mg/kg of midazolam, experienced hypotension at the end of the procedure. This was reversed with 0.4 mg of Narcan and was attributed to the administration of meperidine.

000106

Two midazolam-treated patients (.045 mg/kg and 0.1 mg/kg) and three diazepam-treated patients experienced an extended period of drowsiness following the completion of the study and were required to remain at the study center for an additional period (up to 100 minutes). In this study, the investigator administered 1 mg/kg of meperidine to all patients.

Two patients who received midazolam had evidence of venous irritation on the follow-up examination.

Most changes in vital signs were transient and were most often associated with the gastroscopy. Changes were usually mild to moderate with severe changes only occurring for an increase in pulse rate. One midazolam-treated patient had a severe increase in pulse rate during maintenance, and patient who received diazepam, had a severe increase in pulse rate both during induction and maintenance.

Summary and Conclusions

This randomized, double-blind study compared the use of I.V. midazolam and I.V. diazepam as adjuncts to intramuscular meperidine and local anesthetic administration for the production of sedation for gastroscopy. Both agents were effective. Assessments of sedation by both the physician and patients were in most instances "good" to "excellent". All patients after one hour indicated that they would elect to undergo the procedure the same way again and only 1 midazolam patient changed his opinion on the following day.

Recovery from sedation showed similar patterns in both groups. Impairment of recall of the gastroscopy was induced in most patients in both groups.

A remotely related to midazolam myocardial infarction was detected on follow-up examination as were three cases of venous irritation. There were two in midazolam patients and one in a diazepam patient.

Hypotension was noted in one midazolam patient and was attributed to meperidine. Several patients in both groups experienced extended periods of drowsiness which may have been related to a 1 mg/kg dose of meperidine administered with the benzodiazepine.

000109

Study No. 104

Title: A Comparison of Midazolam and Diazepam in Combination with Meperidine During Local Anesthesia for Gastroscopy

Investigator: John F. Morrissey, M.D.

Objective:

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in 20 adults undergoing gastroscopy for the first time.

Subjects

Twenty patients (ASA I or II) undergoing diagnostic gastroscopy for the first time. The study population was comprised of 10 non-pregnant females and 10 males ranging in age from 20 to 76 years. In the midazolam group there were 2 males and 8 females with a mean age of 45.2 years (range 20-76). In the diazepam group there were 8 males and 2 females with a mean age of 46.4 years (range 21-65).

Study Drugs

Approximately 30 minutes before the gastroscopy, meperidine 50-75 mg and atropine 0.5 mg were administered intramuscularly. Following topical anesthetic administration, 5.0-7.5 mg of either midazolam or diazepam were administered intravenously over a 2-3 minute period. Elderly patients received 2.50-3.75 mg of the test medications over the same time interval. Incremental doses (25% of initial dose) were administered, if necessary, until the patient's speech became thickened and slurred but the patient was still responsive to verbal commands.

Experimental Design

Immediately following the gastroscopy, the blinded physician evaluated as excellent, good, fair or poor the sedative effects produced by the test medication. The assessments included (1) patient cooperation, (2) muscle relaxation, (3) ease of endoscopic examination, (4) control of gag reflex, (5) control of laryngospasm, (6) control of cough reflex, (7) control of retching and vomiting, (8) control of salivation and (9) overall tolerance of the procedure. One hour after gastroscopy and one day later in a follow-up questionnaire, patients evaluated the sedation during the procedure as excellent, good, fair or poor. In addition on both occasions, patients were asked if they would elect to undergo a future gastroscopy the same way, if necessary. One hour after gastroscopy patients evaluated the procedure as not painful, somewhat painful or very painful and whether they could recall none, some or all of the gastroscopy. In the follow-up questionnaire, patients were also asked whether they could recall clearly, vaguely or not at all events before, during and after gastroscopy.

000110

Recovery from sedation was assessed by the Trieger Test which was completed by the patient before medication (baseline) and at 60 and 120 minutes following the completion of the gastroscopy. Each Trieger Test was evaluated for the number of dots missed and the total deviation (mm) from the dots.

Vital signs were monitored before, during and after gastroscopy. Changes in vital signs greater than 20% from baseline were identified as possible adverse experiences. The severity of the changes was categorized as:

mild - a change $\geq$ 20 percent but $<$ 30 percent from baseline
moderate - a change $>$ 30 percent but $<$ 50 percent from baseline
severe - a change $\geq$ 50 percent from baseline or treatment required

Adverse experiences were further categorized according to the phase of the study as induction, maintenance (gastroscopy) and recovery. Seven to 14 days following the study the intravenous injection site was examined for tenderness, redness and induration.

Results

Induction of Intravenous Sedation

Comparable levels of sedation were achieved with mean doses of 0.10 mg/kg of midazolam and 0.173 mg/kg of diazepam. Midazolam-treated patients required a significantly shorter mean time to reach the sedative end point than diazepam-treated patients (3.65 vs. 6.67 minutes).

Physician's Assessment

In most instances the assessment of sedation was "good" to "excellent" for both groups of patients. There were no significant differences between treatments.

Patient's Assessment

On both evaluation occasions (one hour after the procedure and the following day), all patients rated the sedation produced by midazolam or diazepam as "good" to "excellent." One hour after the procedure 9 of 10 midazolam patients and all of the diazepam patients responded that they would elect to undergo the procedure the same way again. By the following day this response was unanimous. Both test groups indicated that there was little or no pain associated with the gastroscopy.

Trieger Test

There were no statistically significant differences between groups in recovery from sedation. More dots were missed by the midazolam group one hour following the gastroscopy than by the diazepam group. This was true for total deviation from the dots as well. By two hours the results were returning to near baseline value.

000111

Follow-up Questionnaire for Amnesia

The responses of one diazepam-treated patient to recall the one and two hour Trieger Tests were not analyzed. This patient remembered doing the Trieger Test only once after the procedure but did not know whether it was the one or two hour test. All patients recalled the procedures prior to being sedated. Lack of recall of the scope introduction and withdrawal was induced in all midazolam and most diazepam patients. This period was extended to one hour in half of the midazolam-treated patients, while the majority of the diazepam patients recalled their one hour Trieger Test.

Safety

Adverse experiences were limited to vital sign changes and venous irritation. Most changes in vital signs were transient and were most often associated with the gastroscopy. Several midazolam-treated patients had severe increases in pulse rate, while several diazepam-treated patients had severe increases in both respiration and pulse rate.

Patient . . . who received midazolam, had evidence of venous irritation for one week following the procedure. The injection site showed signs of tenderness, redness and induration. Patient . . . who received diazepam, also had tenderness and induration at the injection site on the follow-up examination.

Summary and Conclusions

This randomized, double-blind study compared the use of IV midazolam and IV diazepam as adjuncts to intramuscular meperidine and local anesthetic administration for the production of sedation for gastroscopy. Both agents were effective. Assessments of sedation by both the physician and the patients were "good" to "excellent" in most instances. By the following day, all patients indicated they would elect to undergo the procedure the same way again.

Midazolam-treated patients had less recall of events during and following the gastroscopy than did patients in the diazepam group. Midazolam patients had more impairment of psychomotor performance one hour following the procedure than diazepam patients, although the difference was not statistically significant. Changes in vital signs were not clinically significant. Venous irritation was noted in one patient from each treatment group.

This study showed that midazolam, when used in combination with meperidine and a topical anesthetic agent, is as safe and effective as diazepam in inducing sedation for gastroscopy. Midazolam may have been a better agent for the induction of impaired recall of operative and post-operative events.

Study No. 109, Protocol 2241A

Title: A Comparison of Midazolam and Diazepam as Intravenous Sedation for Elective, Direct-Current Cardioversion

Investigator: Tennyson G. Lee, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in patients undergoing elective, direct-current cardioversion for supraventricular tachyarrhythmias.

Subjects

There were only five subjects entered into the study at the time of submission. There was one midazolam-treated patient, age 30. There were four diazepam-treated patients aged 57-81.

Study Drugs

The investigator titrated slowly the initial and incremental doses of either midazolam or diazepam (5-15 mg) until the patient's speech became slurred and thickened but the patient was still responsive to verbal commands. In addition, 1-5 mg of test medication was administered if the investigator felt that the patients required more sedation prior to electrocardioversion.

Experimental Design

This was a randomized, double-blind, parallel group study. The initial and subsequent countershock energy levels were determined by the investigator. The drug dose and time required to induce sedation were calculated. The drug effects were assessed by both the physician and the patient. Immediately following the cardioversion, the physician evaluated (a) quality of sedation, (b) patient's cooperation, (c) muscle relaxation, and (d) patient's overall tolerance of the procedure. One hour after cardioversion and one day later in a follow-up questionnaire, patients evaluated (a) quality of sedation, (b) pain during the procedure, (c) memory of the procedure, and (d) whether they would elect to undergo a future cardioversion, if necessary, the same way.

Recovery from sedation was assessed by the Trieger Test which was completed by the patient before medication (baseline) and at 60 and 120 minutes following the completion of cardioversion. Each Trieger Test was evaluated for the number of dots missed and the total deviation (mm) from the dots.

Continuous electrocardiographic monitoring was done before, during and after completion of the procedure while the patient was in the procedure or recovery room. Blood pressure, respiratory rate and pulse rate were monitored before, during and after cardioversion. Significant changes in vital signs from baseline, were identified as possible adverse experiences (mild: $\geq 20\%$ but $< 30\%$ change; moderate $\geq 30\%$ but $< 50\%$ change; and severe $\geq 50\%$ change from baseline). The intravenous injection site was examined 7-14 days following the procedure for possible venous irritation.

Results

Drug Dose and Time Required to Induce Sedation

The one midazolam patient received 0.136 mg/kg to induce sedation and induction time was 3 minutes. The four diazepam patients received from 0.064 mg to 0.122 mg/kg to induce sedation and induction time was 2 to 5.93 minutes.

Physician's Assessment

The midazolam patient rated "excellent" to "good" on all parameters. Midazolam treatment was rated "excellent" on about half the parameters in each case and "poor" to "good" on the others with no pattern developing.

Patient's Assessment

The quality of sedation was rated as "excellent" by all five patients. Twenty-four hours after cardioversion, none of the five patients had any recall of the procedure and at one hour only one diazepam patient had any recall.

Trieger Test

Two diazepam patients missed more dots on both tests after cardioversion and had more deviation than at the baseline measurement. Midazolam patient missed more dots and had more deviation on the one hour test, but, at two hours, he missed fewer dots than on the baseline measurement.

Safety

Patient _____ who received midazolam had transient apnea with spontaneous improvement. Cardioversion was carried out with no problems. A similar apnea problem was observed in patient _____ who received diazepam. Respiratory rate, pulse rate and mean arterial pressure fluctuated more than 20% from baseline intermittently; however, these changes were transient and clinically insignificant. There was no venous irritation or phlebitis.

Summary and Conclusions

No comparisons are possible since only one midazolam and four diazepam patients were included in this study. There was one incidence of transient apnea in each study group.

Pooled Study Summary
Study Nos. 114, 115, 122, Protocol 2242A

Title: A Comparison of Midazolam and Diazepam With Meperidine Pretreatment for Sedation During Cardiac Catheterization

Subjects

Sixty two patients (ASA I, II or III) undergoing diagnostic cardiac catheterization for the first time participated in the study. The study population consisted of 21 non-pregnant females and 41 males ranging in age from 31 to 68 years. In the midazolam group there were 30 patients comprised of 18 males and 12 females with a mean age of 53.8 years (range 31-68). In the diazepam group there were 32 patients comprised of 23 males and 9 females with a mean age of 51.1 years (range 36-64).

Results

Differences Among Study Centers

The doses of meperidine and of the test medications varied among the three centers. The patients in Study 115 received a relatively higher dose of meperidine; consequently they required lesser amounts of the test medications and a shorter time to induce sedation than the patients in the other two centers.

Deviations from Protocol

These are addressed in the individual study summaries.

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean initial doses of 0.072 mg/kg IV midazolam and 0.092 mg/kg IV diazepam, in respective mean induction times of 4.83 minutes and 8.95 minutes. The midazolam-treated patients required a significantly shorter time and less test drug to attain the sedative end point than the diazepam group.

Physician's Assessment

The mean scores for quality of sedation, muscle relaxation and overall patient tolerance among the midazolam-treated patients were significantly higher than among the diazepam-treated patients.

Patient's Assessment

One hour after the procedure 13 of 30 midazolam patients had complete recollection of the procedure compared with 26 of 30 diazepam patients.

Twenty four hours after the procedure, only 9 of 30 midazolam patients had complete recollection of the procedure compared with 24 of 30 patients in the midazolam group. One hour after the procedure, a greater number of midazolam patients rated the quality of sedation as "excellent" than those in the diazepam group (24 vs. 13). The majority of patients in each group had either no pain or minimal pain during the procedure and would elect to have a future procedure conducted the same way.

Trieger Test

The results of the two groups were comparable at one and two hours following catheterization and the pattern of recovery from sedation was similar for both groups.

Adverse Reactions

Table 1

Clinical Adverse Experiences

	<u>Midazolam (n=30)</u>		<u>Diazepam (n=32)</u>	
	<u># pts.</u>	<u>Percent</u>	<u># pts.</u>	<u>Percent</u>
<u>Possibly and Probably Related Drug Effects</u>				
<u>Respiratory System</u>				
Respiration Rate Increase	10	33.3	14	43.8
Respiration Rate Decrease	12	40.0	11	34.4
<u>Cardiovascular System</u>				
Pulse Increase	14	46.7	10	31.3
Pulse Decrease	7	23.3	6	18.8
MAP Decrease	16	53.3	3	25.0
MAP Increase	0	0	1	3.1
<u>Gastrointestinal</u>				
Acid Taste	1	3.3	0	0
Nausea	1	3.3	0	0
Vomiting	1	3.3	0	0
<u>Central Nervous</u>				
Headache	1	3.3	0	0
<u>Remotely Related Drug Effect</u>				
<u>Cardiovascular</u>				
Asystole	0	0	1	3.1
Tenderness of Vein	0	0	1	3.1
<u>Gastrointestinal</u>				
Nausea	1	3.3	2	6.3
Vomiting	0	0	2	6.3

None of the cardiovascular or respiratory adverse experiences were clinically significant and none required any specific corrective measures. Patients were examined 7-14 days following catheterization and none of the midazolam-treated patients had any clinical evidence of vein irritation or phlebitis at the intravenous injection site.

Summary and Conclusions

In this multicenter study the results of three randomized, double-blind parallel group studies included 62 adults. It was demonstrated that both midazolam and diazepam were effective intravenous sedative agents for cardiac catheterization when used in patients premedicated with meperidine. Comparable levels of sedation (slurred speech) were attained with initial mean doses of 0.072 mg/kg of IV midazolam and 0.092 mg/kg of IV diazepam. The mean time required to attain the sedative end point was 4.83 minutes for midazolam and 8.95 minutes for diazepam.

The physician's assessment showed that the midazolam-treated patients were significantly more relaxed, more sedated and had better tolerance of the procedure than the diazepam group. The patient's assessment revealed some superiority of midazolam over diazepam with respect to the quality of sedation. A greater number of midazolam patients had impaired recall of the procedure.

The pattern of psychomotor recovery was similar for both groups. Vital sign fluctuations occurred transiently during catheterization; however, these changes were clinically insignificant and required no corrective measures. Other adverse experiences were of minor nature and infrequent.

This study demonstrated that IV midazolam when used with meperidine as premedicant in cardiac catheterization is as safe as diazepam. It has some superiority in diminishing recall of the procedure and appears to have an earlier onset of action. In the doses employed it effectively provided sedation.

Study No. 114

Title: A Comparison of Midazolam and Diazepam With Meperidine Pretreatment for Sedation During Cardiac Catheterization

Investigator: Goffredo G. Gensini, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam when given in conjunction with meperidine as a premedication, for sedation during cardiac catheterization.

Experimental Design

Randomized, double-blind parallel study in 22 adults undergoing diagnostic cardiac catheterization for the first time. Prior to catheterization midazolam or diazepam was administered by random coded assignment. Immediately following the catheterization, the physician evaluated (a) quality of sedation, (b) patient's cooperation, (c) muscle relaxation, and (d) patient's overall tolerance of procedure. One hour after catheterization and one day later in a follow-up questionnaire, patients evaluated (a) quality of sedation, (b) pain during the procedure, (c) memory of the procedure, and (d) whether they would elect to undergo a future catheterization, if necessary, the same way.

Recovery from sedation was assessed by the Trieger Test which was completed by the patient before medication (baseline) and at 60 and 120 minutes following the completion of catheterization. Each Trieger Test was evaluated for the number of dots missed and the total deviation (mm) from the dots.

Continuous electrocardiograph monitoring was done before, during and after completion of the procedure while the patient was in the catheterization laboratory. Blood pressure, respiratory rate and pulse rate were monitored before, during and after catheterization. Changes in vital signs greater than 20% from baseline were identified as possible adverse experiences. The intravenous injection site was examined 7-14 days following the procedure for possible venous irritation.

Subjects

There were 4 non-pregnant females and 18 males, ranging in age from 36 to 64 years (ASA Class I-III). In the midazolam group there were 10 males and 0 females with a mean age of 56.8 years (range 64-103). In the diazepam group there were 8 males and 4 females with a mean age of 50.7 years (range 36-64).

N-18654-4

Study Drugs

Approximately 30 minutes before catheterization, all patients (except patient - diazepam group) received meperidine 25 mg IM. Patient was excluded from efficacy analyses for procedural complications. Based on the patient's age and clinical condition, the investigator slowly administered (2-3 minutes) the initial and incremental doses (1-10 mg) of either midazolam or diazepam until the patient's speech became slurred and thickened but the patient was still responsive to verbal commands. In addition, 1-5 mg of test medication was administered, if necessary, to maintain adequate sedation during cardiac catheterization.

Results

Deviations from Protocol

Patient - diazepam. Investigator decided to deviate from the protocol, due to his lack of experience with test drug, after administration of 7.5 mg of test medication to the patient. Additional test drug was not given and sedation was not induced as directed in the protocol.

Patient - diazepam. During cardiac catheterization, immediately following ventriculography, patient's electrocardiogram showed ST-segment elevation, progressing to asystole. Investigator felt this to be related to injection of contrast agent used for ventriculography. Patient responded to treatment. Nonetheless, investigator decided to terminate subsequent study procedure.

Patient - diazepam. Could not complete the 2-hour post-catheterization Trieger Test due to nausea and vomiting.

Induction of Intravenous Sedation

Midazolam-treated patients required a mean initial dose of 0.067 mg/kg (range 0.049-0.078) compared to 0.110 mg/kg (range 0.063-0.155) required by the diazepam group. None of the patients required any additional medication to maintain sedation during catheterization. The mean induction time was 7.2 minutes with midazolam and 16.19 minutes with diazepam. The midazolam time was significantly faster.

Physician's Assessment

The quality of sedation, muscle relaxation and patient's overall tolerance in midazolam-treated patients were rated as "excellent" by the physician who performed the catheterization. These ratings were significantly better than those in the diazepam group, rated "fair" to "good."

Patient's Assessment

One hour after completion of the catheterization, only 40% (4 of 10) and on the following day, only 30% (3 of 10) of the midazolam-treated patients could recall the procedure completely, compared with a complete recollection by all patients (10) in the diazepam group. All midazolam patients were pain-free during the procedure, while 3 of 10 diazepam patients experienced some pain. Nine midazolam-treated patients rated the quality of sedation as "good" to "excellent" compared with 7 diazepam patients. In each treatment group all of the patients would elect to undergo a future procedure the same way on the one hour rating. After one day one patient changed this opinion in each group.

Trieger Test

Although the sponsor indicated similar patterns of recovery from sedation for both groups this reviewer disagrees. The midazolam-treated group had greater changes from baseline after one hour, and returned toward baseline at two hours. The diazepam-treated group progressively deteriorated away from the baseline from one to two hours post-catheterization.

Adverse Reactions

Table 1

Clinical Adverse Experiences

	<u>Midazolam</u>		<u>Diazepam</u>	
	<u># pts.</u>	<u>Percent</u>	<u># pts.</u>	<u>Percent</u>
<u>Possibly and Probably Related Drug Effects</u>				
<u>Respiratory System</u>				
Respiratory Rate Increase	1	10	8	66.7
Respiratory Rate Decrease	7	70	7	58.3
<u>Cardiovascular System</u>				
Pulse Increase	4	40	4	33.3
Pulse Decrease	4	40	2	16.7
MAP Decrease	8	80	4	33.3
<u>Gastrointestinal</u>				
Acid Taste	1	10	0	0
Nausea	1	10	0	0
Vomiting	1	10	0	0
<u>Central Nervous</u>				
Headache	1	10	0	0

Relationship to Test Drug - Remote

<u>Cardiovascular</u>				
Asystole	0	0	1	8.3
Tenderness of Vein	0	0	1	8.3
<u>Gastrointestinal</u>				
Nausea	0	0	1	8.3
Vomiting	0	0	1	8.3

The majority of changes from baseline in vital signs were transient and clinically insignificant. None of the midazolam-treated patients experienced any clinically significant respiratory or cardiovascular problems.

Summary and Conclusions

This randomized, double-blind study compared the use of midazolam with diazepam to provide sedation during cardiac catheterization in patients premedicated with meperidine. Midazolam provided "excellent" sedation and was felt by physician and patient to be a superior sedative agent when compared to

diazepam. Recall of the procedure was considerably less in the midazolam-treated group. The mean initial sedative dose of 0.067 mg/kg of IV midazolam and 0.1110 mg/kg of IV diazepam induced adequate sedation in patients premedicated with meperidine. The mean time required to attain slurred speech was 7.2 minutes for the midazolam-treated patients and 16.19 minutes for the diazepam group. The pattern of recovery from sedative effects, as assessed by the Frieger Test showed more progress toward the baseline condition in the midazolam group.

None of the midazolam-treated patients had any clinically significant complications. There were infrequent transient complaints such as nausea, vomiting, headache and "acid-taste." There were no clinically significant cardiovascular or respiratory problems. The results of this study showed that IV midazolam was safe when used to provide sedation during cardiac catheterization in patients premedicated with meperidine and appeared to be superior to IV diazepam with respect to sedation and diminished recall of the procedure.

Study No. 115

Title: A Comparison of Midazolam and Diazepam With Meperidine Pretreatment for Sedation During Cardiac Catheterization

Investigator: Grady G. Hendrix, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam given in conjunction with meperidine as a premedication for sedation during cardiac catheterization.

Experimental Design

Randomized, double-blind parallel study in 20 adults undergoing diagnostic cardiac catheterization for the first time. The design of this study was similar to that of study 114 since this was a multicenter study following the same protocol.

Subjects

There were 17 non-pregnant females and 9 males, ranging in age from 38 to 67 years (ASA Class I-III). In the midazolam group there were 2 males and 8 females with a mean age of 54.6 years (range 43-67). In the diazepam group there were 7 males and 3 females with a mean age of 51.5 years (range 38-61).

Study Drugs: See Study 114.

ResultsDeviations from Protocol

Although the doses of the test drug were specified in the protocol, the investigator adjusted the doses of the initial and subsequent test-drug injections according to the patient's age, weight and overall clinical conditions.

All patients were included in the analyses; however, Trieger Test results of three patients were excluded.

Patient _____ - midazolam. Baseline Trieger Test was not done prior to the test-drug injection as directed in the protocol.

Patient _____ - midazolam. Due to incision in right arm, patient could not do post-catheterization Trieger Tests. Only baseline Trieger Test was available.

Patient _____ - diazepam. Same as patient _____

Patient — midazolam. Could not complete the two-hour post-catheterization Trieger Test due to nausea, the baseline and one-hour post-catheterization results of this patient were analyzed. This patient received 25 mg PO thioridazine approximately 18 hours prior to the test drug administration. It was decided to include the patient in all analyses since she was taking the drug chronically on a daily basis and her case record did not reveal any unusual pattern of results.

Induction of Intravenous Sedation

Midazolam-treated patients required a mean initial dose of 0.051 mg/kg (range 0.028-0.097) to reach the sedative end point compared to 0.057 mg/kg (range 0.017-0.115) required by the diazepam group. Midazolam patients required an additional mean dose of 0.010 mg/kg (range 0-0.040) to maintain adequate sedation during catheterization compared with 0.018 mg/kg (range 0-0.047) required by diazepam-treated patients. The mean total dose for midazolam group was 0.061 mg/kg (range 0.028-0.097) compared with 0.075 mg/kg (range 0.017-0.155) for diazepam. The mean induction time was 2.1 minutes with midazolam and 2.7 minutes with diazepam.

Physician's Assessment

The quality of sedation, muscle relaxation, patient's cooperation and patient's overall tolerance for both midazolam and diazepam groups were rated as "good" to "excellent" by the physician who performed the catheterization.

Patient's Assessment

One hour after completion of catheterization, a greater number of midazolam-treated patients experienced no recall of the procedure than the diazepam group, with only 5 of 10 midazolam patients compared with all 10 diazepam patients having a complete recollection of the procedure. In both groups patients experienced either no pain at all or minimal pain. The quality of sedation was rated as "good" to "excellent" by both groups, with 1 patient in each group giving a "fair" rating. Eight of ten of the midazolam and nine of ten diazepam-treated patients would undergo the procedure the same way again.

Trieger Test

The pattern of recovery from sedation was similar for both groups of patients.

Adverse Reactions

Respiratory rate decreased in 20% of the midazolam-treated and 10% of the diazepam-treated patients; however, during the same period, respiratory rate increased in 20% of the patients in each group. Most of these changes were mild, transient and clinically insignificant and none of the patients required any specific corrective measures. Minor transient fluctuations in blood pressure and pulse rate were noted during catheterization--these changes are not uncommon during cardiac catheterization.

Patient - in the midazolam group had transient nausea approximately two hours after completion of catheterization which, according to the investigator was not related to the test drug. No other adverse reactions were noted. Patients were examined 7-14 days following catheterization and no patient had clinical evidence of vein irritation or phlebitis at the intravenous injection site.

Summary and Conclusions

This randomized double-blind study compared the use of midazolam with diazepam to provide sedation during cardiac catheterization in patients premedicated with meperidine. Midazolam and diazepam both provided "good" to "excellent" sedation in the majority of patients during cardiac catheterization. The mean initial sedation doses were comparable and induced adequate sedation. The initial dose was 0.057 mg/kg of IV diazepam and 0.051 mg/kg of IV midazolam. The mean induction time was 2.7 minutes and 2.1 minutes respectively. One hour after completion of cardiac catheterization, midazolam patients had less recall of the procedure than the diazepam group. Patterns of psychomotor recovery were similar for both groups.

There were no significant adverse reactions in this study. The results of this study showed that IV midazolam was safe when used to provide sedation during cardiac catheterization in patients premedicated with meperidine and was as effective as IV diazepam while providing for less recall of the procedure in some cases.

Study No. 122

Title: A Comparison of Midazolam and Diazepam With Meperidine Pretreatment for Sedation During Cardiac Catheterization

Investigator: Philip A. Ludbrook, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam given in conjunction with meperidine as a premedication for sedation during cardiac catheterization.

Experimental Design

Randomized, double-blind parallel study in 20 adults undergoing diagnostic cardiac catheterization for the first time. The design of this study was similar to that of study 114 since this was a multicenter study following the same protocol.

Subjects

There were 6 non-pregnant females and 14 males, ranging in age from 31 to 68 years (ASA Class I-III). In the midazolam group there were 6 males and 4 females with a mean age of 50.1 years (range 31-68). In the diazepam group there were 8 males and 2 females with a mean age of 51.1 years (range 42-59).

Study Drugs: See Study 114.

ResultsDeviations from Protocol

Although the doses of meperidine and the test drug were specified in the protocol, the investigator adjusted the doses of these medications according to the patient's age, weight and overall clinical status. Otherwise, there were no significant deviations from the protocol. All patients were included in all analyses.

Induction of Intravenous Sedation

Midazolam-treated patients required a mean initial dose of 0.097 mg/kg (range 0.075-0.112) to reach the sedative end point compared to 0.110 mg/kg (range 0.079-0.197) required by the diazepam group. Midazolam-treated patients required an additional dose of 0-0.083 mg/kg to maintain adequate sedation during catheterization compared with 0.013-0.080 mg/kg required by diazepam-treated patients. The mean total dose for midazolam patients was 0.124 mg/kg compared with 0.142 mg/kg for diazepam. The mean time required to attain the sedative end point was 5.2 minutes for the midazolam patients and 8.0 minutes for the diazepam group.

Physician's Assessment

Midazolam-treated patients had significantly higher scores than the diazepam-treated group with respect to quality of sedation and patient tolerance. The quality of sedation, muscle relaxation, patient's cooperation and patient's overall tolerance were rated as "excellent" for the majority of midazolam patients. The corresponding ratings were "good" to "excellent" for the diazepam group.

Patient's Assessment

At 24 hours after catheterization, a greater number of midazolam-treated patients experienced less recall of the procedure than the diazepam group; however, this difference was not seen at the one-hour post-catheterization evaluation. In both groups minimal or no pain was experienced and the quality of sedation was rated as "good" to "excellent." All patients would have the procedure performed the same way again.

Trieger Test

The pattern of recovery from sedation was similar for patients in both groups.

Adverse Reactions

Changes in vital signs were transient and clinically insignificant. None of the patients required any corrective measures. There were no significant differences between the two groups. None of the patients had any clinically significant respiratory depression or hypotension.

Patient - diazepam had transient nausea and vomiting following catheterization and, according to the investigator this was related to the contract media utilized during catheterization. No other adverse reactions were noted. Patients were examined 7-14 days following catheterization and no patient had clinical evidence of vein irritation or phlebitis at the intravenous injection site.

Summary and Conclusions

This randomized, double-blind study compared the use of midazolam with diazepam to provide sedation during cardiac catheterization in patients premedicated with meperidine. A mean initial sedation dose of 0.097 mg/kg of IV midazolam and 0.110 mg/kg of IV diazepam induced adequate sedation in mean times of 5.2 and 8 minutes, respectively. The physician's assessment revealed that midazolam-treated patients were significantly more sedated and had better tolerance of the procedure than the diazepam group.

In both groups, the patients rated the quality of sedation as "good" to "excellent." Twenty four hours after catheterization, a greater number of midazolam-treated patients experienced partial or no recall of the procedure than in the diazepam group.

There were no significant adverse experiences in this study. These transient fluctuations in vital signs, but these were clinically insignificant and did not require any corrective measures. The results of this study showed that IV midazolam was safe when used to provide sedation during cardiac catheterization in patients premedicated with meperidine and was as effective as IV diazepam while providing for less recall of the procedure in some cases.

Study No. 009, Protocol 1032

Title: Comparison Between Diazepam and Midazolam of Cardiovascular and Sedative Effects during Cardiac Catheterization

Investigator: Robert J. Fragen, M.D.

Objective

This study was designed to compare the cardiovascular effects of intravenous midazolam with diazepam and saline in patients undergoing cardiac catheterization for suspected coronary artery disease.

Experimental Design

Randomized, double-blind parallel study in thirty adults undergoing cardiac catheterization. Patients had stable angina pectoris and were unpremedicated. They were randomly assigned to three groups: 10 midazolam, 10 diazepam and 10 normal saline. A Swan-Ganz thermodilution catheter was inserted to measure pulmonary capillary wedge pressure, right atrial pressure and cardiac output. A catheter was inserted to measure aortic pressure, cardiac index, systemic vascular resistance and left ventricular stroke work index were calculated using standard formulae.

Degree of sedation was assessed on a 4-point scale: 0 = none, 1 = mild, 2 = moderate, 3 = marked. Bolus injections of midazolam 0.05 mg/kg, diazepam 0.10 mg/kg or saline 0.02 ml/kg were administered intravenously. All hemodynamic measurements were made under baseline, control pre-treatment conditions and at 5 and 15 minutes after test drug injection. Respiration rate was also recorded at baseline and 5 and 15 minutes after injection. Changes in vital signs were evaluated according to the following criteria.

Mild = $\geq 20\%$ but $< 30\%$ change from control
Moderate = $\geq 30\%$ but $< 50\%$ change from control
Severe = $\geq 50\%$ change from control

Subjects

There were 30 patients ranging in age from 35 to 66. In the midazolam group there were 7 males and 3 females with a mean age of 50.4 (range 35-62). In the diazepam group there were 8 males and 3 females with a mean age of 56.4 (range 48-66). In the saline group there were 10 males and no females with a mean age of 48.7 (range 35-59).

Study Drugs

There were three groups of patients: Each group consisted of 10 patients. Bolus injections of either diazepam 0.10 mg/kg, midazolam 0.05 mg/kg or saline 0.02 ml/kg were administered by an intravenous injection into a free running IV fluid line over one minute. The contents of the injection were unknown to the patient and the catheterization team.

Results

Deviations from Protocol

The investigator utilized a randomized code generated at his institution rather than that supplied by the sponsor.

Hemodynamic Parameters

1. Left ventricular function:

There were no significant differences between midazolam and diazepam in parameters of left ventricular function (cardiac output, cardiac index, stroke index, stroke volume, left ventricular stroke work index). Significantly greater decreases were observed with midazolam than saline in stroke volume at 5 minutes and 15 minutes and in left ventricular stroke work index at 15 minutes; however, these were not major alterations.

2. Vital signs: With respect to vital signs, there was a greater decrease in systolic blood pressure with midazolam than saline at 15 minutes; however, no changes in vital signs were significantly different between groups. In only one instance did the change from baseline exceed 20% (increased mean arterial pressure in one diazepam-treated patient).

3. Pressures (pulmonary arterial systolic, pulmonary arterial diastolic, mean pulmonary artery, pulmonary capillary wedge and right atrial pressure): The only change to reach significance was a greater decrease in pulmonary capillary wedge pressure, at 15 minutes with midazolam than saline, but this was of small magnitude. There were no significant differences between midazolam and diazepam.

4. Resistance (total systemic, total pulmonary, pulmonary arteriolar resistances): No significant differences between midazolam and diazepam were noted.

5. Arterial blood gases (O_2 , pH, pO_2 , pCO_2 , O_2 saturation, HCO_3 , base excess) and venous blood gases (pH, pO_2 , pCO_2 , O_2 content, venous HCO_3 , base excess, O_2 saturation): There were isolated differences between midazolam and diazepam and between midazolam and saline; however, there was no consistent trend nor any clinically significant effect.

6. Sedation: At five and fifteen minutes patients who received midazolam or diazepam were more sedated than those who received saline, and midazolam patients were significantly more sedated than were diazepam patients. Following injection approximately half the diazepam-treated patients were mildly sedated at 5 and 15 minutes, while only one saline-treated patient was mildly sedated. With midazolam, 8 out of 10 patients were mildly or moderately sedated at 5 and 15 minutes, the remainder being unsedated.

Safety

Midazolam: There were no adverse reactions.

Saline: One patient had a period of bigeminy about 2 to 3 minutes after injection lasting approximately 20 to 30 seconds.

Diazepam: Patient reported slight dizziness just after injection, felt to be probably drug related. Ventricular fibrillation occurred in patient during the angiogram, and he was easily defibrillated with no subsequent effects. This was considered remotely drug related, since it occurred later in time than the peak effect of the drug. Patient #015 had mildly increased mean arterial pressure during the procedure, considered remotely drug related.

Summary and Conclusions

This was a randomized, double-blind, parallel group evaluation of midazolam sedative and hemodynamic effects during cardiac catheterization. Measurement of changes from control values in hemodynamic parameters were compared between midazolam and saline. There were no statistically significant differences between midazolam and diazepam in any parameter.

The mean degree of sedation did not reach the moderate level in any group. Most patients in the midazolam group and half of the diazepam patients reached a mild level of sedation.

The only probably drug-related adverse reaction was dizziness reported by one diazepam patient. There was no venous irritation. changes in vital signs were not significant.

This study demonstrated that midazolam was a safe and effective intravenous sedative to use in patients with stable coronary artery disease undergoing cardiac catheterization. Cardiac hemodynamics were minimally altered to a clinically insignificant degree.

Pooled Study Summary

Study Nos. 103 and 111, Protocol 2243A

Title: A comparison of Midazolam and Diazepam for Intravenous Sedation During Angiography

Subjects

Thirty five patients undergoing coronary angiography were the subjects of this study. In the midazolam group there were 13 subjects consisting of 11 males and 7 females with a mean age of 52.4 years (range 28-62). In the diazepam group there were 17 subjects consisting of 11 males and 6 females with a mean age of 53.5 years (range 17-73).

ResultsDifferences Between the Centers

The patients in study 103 received relatively higher midazolam and lower diazepam doses than the patients in study 111. A relatively shorter procedural time also existed in study 103. Consequently, the patients in study 103 performed the one and two hour postangiography Trieger Tests about one-half hour earlier on the average than the patients in study 111. Therefore, the evaluation of recovery from sedation for the patients in study 103 could have been affected by a higher total dose of midazolam and an earlier assessment of the recovery after midazolam administration. This might explain the differing Trieger Test results at the two centers. In study 103 the midazolam-treated patients recovered slower than the diazepam group as measured by the Trieger Test; whereas, in study 111 the reverse relationship occurred.

Drug Dose and Time Required to Induce Sedation

The midazolam-treated patients required a significantly shorter time and less test medication than the diazepam group. Respective initial mean sedation doses were 0.121 mg/kg and 0.212 mg/kg and mean induction times were 3.5 minutes and 8.36 minutes.

Physician's Assessment

The quality of sedation, patient cooperation, muscle relaxation and patient tolerance were rated as "good" to "excellent" for both groups. There were no significant differences between groups.

Patient's Assessment

More midazolam patients had impaired recall of the procedure than in the diazepam group. The majority of midazolam-treated patients either had no

recall or partial recall of the procedure at one and 24 hours following angiography at one hour and 24 hours after the procedure, a greater number of patients in the midazolam group rated the quality of sedation as "excellent" than the diazepam group. The majority of patients in both groups preferred to have the procedure performed the same way again, if necessary.

Trieger Test

Differences between centers have been elaborated upon. When the results were pooled, the patterns of recovery were similar for both groups.

Safety

All changes in vital signs from baseline were transient and clinically insignificant. Patient of study 111 (midazolam) developed confusion, disorientation, amnesia and anxiety in the middle of his procedure. This lasted for one hour and he recovered spontaneously. Patient of study 111 (midazolam) had transient apnea, followed by confusion and disorientation for 1/2 hour which resolved spontaneously. Three diazepam-treated patients developed mild phlebitis or vein irritation at the IV site. There was no vein irritation or phlebitis in the diazepam group.

Summary and Conclusions

In this multicenter study midazolam was used to provide sedation during coronary angiography. Midazolam-treated patients required a mean initial sedation dose of 0.121 mg/kg and a mean induction time of 3.5 minutes compared with a mean initial sedation dose of 0.212 mg/kg and a mean time of 8.36 minutes required by the diazepam group to reach the sedative end point. The physician's assessment indicated no significant differences between the two drugs; however, the patient's assessment revealed that a greater number of patients in the midazolam group experienced diminished recall of the procedure and rated the quality of sedation as "excellent."

The pooled results indicated similar patterns of psychomotor recovery from sedation in the two groups although an apparent prolongation of recovery in the midazolam group in one study could have been related to a higher total dose of midazolam coupled with an earlier assessment time related to a shorter procedure time. Recovery from the sedative effects may be dose-dependent.

All changes in vital signs were transient and clinically insignificant. Two midazolam-treated patients developed confusion and one of these experienced brief apnea; however, both recovered spontaneously. Three diazepam-treated patients developed mild phlebitis or vein irritation at the IV site.

The results of this study showed that IV midazolam is as effective as diazepam as a sedative in coronary angiography. It may have an earlier onset of action than IV diazepam and had no venous irritation. It was safely employed and demonstrated some possibly dose-related delay in recovery from its sedative effects.

Study No. 103

Title: A Comparison of Midazolam and Diazepam for Intravenous Sedation During Angiography

Investigator: Philip A. Ludbrook, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in patients undergoing coronary angiography for the first time.

Subjects

There were 10 non-pregnant females and 12 males, ranging in age from 17 to 73 years (ASA I, II or III). In the midazolam-treated group there were 6 males and 6 females with a mean age of 52.3 years (range 28-62). In the diazepam group there were 6 males and 4 females with a mean age of 54.1 years (range 17-73).

Study Drugs:

Patients were randomly assigned to midazolam or diazepam treatment groups. Based on the patient's age and clinical condition, the investigator slowly titrated (2-3 minutes) the initial and incremental doses (1-10 mg) of either drug until the patient's speech became slurred or thickened but the patient was still responsive to verbal commands. An additional 1-5 mg of test medication was administered, if necessary, to maintain adequate sedation during angiography.

Experimental Design

This was a randomized, double-blind parallel group study. The drug dose and time required to induce sedation were calculated. Drug effects were assessed by the physician and the patient. Immediately following angiography, the physician assessed (a) patient's cooperation, (b) muscle relaxation, (c) quality of sedation and (d) patient's overall tolerance of the procedure. One hour after angiography and one day later patients evaluated (a) quality of sedation, (b) pain during the procedure, (c) memory of the procedure, and (d) whether they would elect to undergo a future angiography, if necessary, the same way. Recovery from sedation was assessed by the Trieger Test which was completed by the patient before medication (baseline) and at 60 and 120 minutes following the completion of angiography. Each Trieger Test was evaluated for the number of dots missed and the total deviation (mm) from the dots.

Continuous electrocardiographic monitoring was carried out in the angiography laboratory. Vital signs were monitored before, during and after angiography. Significant changes from baseline in vital signs were identified as possible adverse experiences (mild: 7, 20% but 30% change; moderate: 30% but 50% change; and severe; 50% change from baseline). The intravenous injection site was examined 7-14 days following the procedure for possible venous irritation.

Results

Deviations from Protocol

Protocol deviations were observed in four patients. Two patients had a history of previous angiographic procedure (patients - midazolam) and were excluded from efficacy analyses. A 17 year old patient (diazepam) met all protocol requirements except for age and was included in all analyses. A fourth patient (midazolam) had surgery 5 to 6 hours after angiography and could not complete the 24 hour post-angiography evaluation. Available data were included in all analysis possible for this patient.

Drug Dose and Time Required to Induce Sedation

Comparable initial levels of sedation were reached by mean doses of 0.144 mg/kg of midazolam and 0.183 mg/kg of diazepam. The sedative end point was attained in a mean time of 4.4 minutes with midazolam and 6.8 minutes with diazepam. Midazolam-treated patients required an additional mean dose of 0.037 mg/kg to maintain adequate sedation compared with 0.056 mg/kg for the diazepam group. The mean total sedation dose was 0.18 mg/kg for the midazolam group and 0.239 mg/kg for the diazepam group.

Physician's Assessment

The quality of sedation, muscle relaxation, patient's cooperation, and overall tolerance were rated as "good" to "excellent" in both treatment groups.

Patient's Assessment

At one hour and 24 hours following angiography, the majority of midazolam-treated patients had no recall or only partial recall of the procedure. A greater number of midazolam patients experienced diminished recall of the procedure than in the diazepam group. The quality of sedation was rated "excellent" by both groups. All patients in both groups preferred to have the procedure performed the same way again and both test groups reported little or no pain associated with the angiography.

Trieger Test

At two hours following angiography midazolam patients missed significantly more dots than the diazepam group. At two hours the diazepam group was recovered according to the two parameters in this test, whereas, the midazolam group still had elevated values compared to baseline.

Safety

The only adverse experiences were changes in vital signs. Most changes in vital signs were transient and clinically insignificant. None of the patients required any corrective measures. None of the patients had any clinically significant respiratory depression or hypotension. There were no clinically significant changes between treatments. No patient had clinical evidence of vein irritation or phlebitis at the intravenous injection site.

Summary and Conclusions

This randomized, double-blind study compared the use of intravenous midazolam with IV diazepam to provide sedation during coronary angiography. Midazolam provided "good" to "excellent" sedation and was equally effective as diazepam. Midazolam patients required 0.144 mg/kg to reach the sedative end point compared with 0.183 mg/kg required by the diazepam group. Comparable levels of sedation were achieved in 4.4 minutes with midazolam and 6.8 minutes with diazepam. At one hour and 24 hours following the procedure, a greater number of midazolam patients had impairment of recall of the procedure than diazepam patients. Recovery from sedation, as measured by the Trieger Test, was slower in the midazolam group. There were no clinically significant adverse experiences in either group in this study. The results of this study showed that IV midazolam was safely used to provide sedation and was as effective as diazepam.

Study No. 111

Title: A Comparison of Midazolam and Diazepam for Intravenous Sedation During Angiography

Investigator: Thomas J. Ryan, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in patients undergoing coronary angiography for the first time.

Subjects

There were 13 patients (ASA I, II, and III) in the study which was still in progress at the time of submission. There were 5 males and 1 female in the midazolam group with a mean age of 52.7 years (range 45-61). In the diazepam group there were 5 males and 2 females with a mean age of 52.7 years (range 44-62).

Study Drugs: See Study 103.

Experimental Design: See Study 103.

ResultsDeviations from Protocol

Patient (diazepam) was found to have significant left main trunk coronary artery disease and underwent emergency surgery. The investigator could not complete the proper subsequent follow-up of the patient; however, available data was analyzed.

Drug Dose and Time Required to Induce Sedation

Comparable initial levels of sedation were reached by mean doses of 0.098 mg/kg of midazolam and 0.242 mg/kg of diazepam. One patient in the midazolam-treated group and three diazepam-treated patients required an additional 0.009 mg/kg and 0.025 mg/kg of drug, respectively, during angiography to maintain adequate sedation. The sedative end point was attained in 2.63 minutes with midazolam and 9.93 minutes with diazepam. The midazolam-treated patients required a significantly shorter time and smaller amount of test drug to attain the sedative end point than the diazepam group.

Physician's Assessment

The quality of sedation, patient's cooperation, muscle relaxation and patient's tolerance were rated as "good" to "excellent" for both groups. There were no significant differences between groups.

Patient's Assesement

One hour following angiography, all six midazolam patients rated the quality of sedation as "excellent" compared with only 3 out of 7 diazepam-treated patients. One hour following angiography, a greater number of patients in the midazolam group had impaired recall of the procedure (5 of 6) than diazepam patients (1 of 7). By 24 hours, the diazepam group added one patient with impaired recall. Little or no pain was experienced by all patients reporting in both groups. All midazolam patients would elect to undergo a future procedure the same way while 2 of 6 repondents answered negatively at 24 hours in the diazepam group.

Trieger Test

Midazolam-treated patients missed fewer dots and had less deviation at one and two hours following angiography than on the baseline test. Diazepam-treated patients missed more dots and had more deviation than on the baseline test.

Safety

Table 1

Clinical Adverse Experiences

	<u>Number of Patients</u>	
	<u>Midazolam</u>	<u>Diazepam</u>
<u>Relationship to Test Drug - Possible or Probable</u>		
<u>Miscellaneous</u>		
Amnesia	1	0
Confusion	2	0
Anxiety	1	0
<u>Integumentary</u>		
Phlebitis at injection site	0	1
Pain during injection	0	1
<u>Respiratory</u>		
Itching Nose	0	1
Apnea	1	0
Respiration Rate Increase	5	4
Respiration Rate Decrease	5	5
<u>Cardiovascular</u>		
Pulse Increase	2	2
Pulse Decrease	0	1
MAP Decrease	3	7
Phlebitis	0	1
Hematoma at IV site	0	1
Tenderness of Vein	0	2
Redness of vein	0	1
Induration of Vein	0	1
<u>Relationship to Test Drug - Remote</u>		
<u>Gastrointestinal</u>		
Vomiting	1	0

Patient ___ (midazolam .144 mg/kg) became confused and disoriented in the middle of the procedure. He also developed amnesia for the events of the preceding weeks and acute anxiety. The episode lasted for approximately one hour; however, the procedure was completed and he recovered spontaneously. Patient ___ (midazolam .068 mg/kg) had transient apnea approximately 4 minutes after the administration of the test drug. She did not require corrective

treatment. Subsequently, she became confused and disoriented for approximately 1/2 hour. She recovered spontaneously with no sequelae. Three diazepam patients (4, 7, 13) developed mild phlebitis or vein irritation at the IV site. Respiratory rate, pulse rate and mean arterial pressure fluctuated more than 20% from baseline intermittently; however, these changes were transient and clinically insignificant. None of the patients in either group had any clinically significant cardiovascular problems, except for the phlebitis described above.

Summary and Conclusions

This randomized, double-blind study compared the use of intravenous midazolam with IV diazepam to provide sedation during coronary angiography. This study was still in progress at the time of submission. Thirteen patients were included in this report. The midazolam-treated patients required a significantly shorter time and less amount of test drug to induce sedation than the diazepam group. The sedative end point was achieved with 0.098 mg/kg of midazolam in 2.63 minutes for the average patient compared with 0.242 mg/kg of diazepam in 9.93 minutes. The physician's assessment showed no significant difference between the two test medications. A greater number of midazolam patients rated the quality of sedation as "excellent" and experienced impaired recall of the procedure than the diazepam group. Recovery from sedation, as measured by the Trieger Test, was slower in the diazepam group. Patient (midazolam) experienced a transient episode of confusion, anxiety and retrograde amnesia; however, recovery was spontaneous and did not hamper the procedure. Patient (midazolam) experienced transient apnea followed by a brief period of confusion; however, recovery was spontaneous and the procedure was completed. Three diazepam-treated patients developed mild phlebitis or vein irritation at the IV site. Vital signs changes were transient and clinically insignificant.

The study showed that IV midazolam was a somewhat better sedative than diazepam, producing more impairment of recall of the procedure. There was less irritation at the IV site than in the diazepam group.

Overall Evaluation and ConclusionsEffectiveness

The clinical investigation of midazolam, when administered intravenously as an adjunct to local anesthetic agents, evaluated the safety and effectiveness of the drug for inducing sedation (slurred speech) in patients undergoing diagnostic endoscopic or cardiovascular procedures. The endoscopic procedures included bronchoscopy, gastroscopy and cystoscopy. The cardiovascular procedures included cardiac catheterization and angiography. Some of the parameters evaluated included sedation, patient cooperation, degree of pain associated with the procedure, amnesia and recovery from sedation. The dose required to reach the sedative end point of slurred speech and time to induction were also recorded.

The sedative properties of midazolam were evaluated in 30 clinical studies involving 749 patients who received midazolam (330 patients), diazepam (336 patients), placebo (73 patients), or normal saline (10 patients). In all studies, diazepam served as the reference drug. In addition, two protocols (2237A and 2237B) also specified placebo reference groups.

TABLE I
NUMBER OF PATIENTS

INVESTIGATOR	STUDY #	TOTAL	MIDAZOLAM	DIAZEPAM	PLACEBO (MIDAZOLAM)	PLACEBO (DIAZEPAM)	OTHER
<u>Protocol 2234A - Bronchoscopy without Meperidine Premedication</u>							
*Steinberg, H.	106	40	20	20	--	--	--
Robertson, J.K.	109	16	8	8	--	--	--
Amad, M.	112	4	3	1	--	--	--
Kvale, P.A.	121	23	11	12	--	--	--
<u>Protocol 2235A - Bronchoscopy with Meperidine Premedication</u>							
*Khan, F.A.	107	22	12	10	--	--	--
*Salchun, O.J.	117	21	10	11	--	--	--
*Jenkinson, S.J.	118	21	10	11	--	--	--
*Sriencheck, W.I.	123	24	11	13	--	--	--
<u>Protocol 2236A - Cystoscopy without Meperidine Premedication</u>							
*Lawson, R.K.	105	43	22	21	--	--	--
Evans, A.T.	113	28	13	15	--	--	--
*Wain, A.J.	119	40	20	20	--	--	--
*Chasapakis, G.	150	40	20	20	--	--	--
<u>Protocol 2237A - Cystoscopy with Meperidine Premedication (Females)</u>							
*Witherington, R.	116	40	10	10	10	10	--
*Witherington, R.	126	10	2	3	3	2	--
<u>Protocol 2237B - Cystoscopy with Meperidine Premedication (Males)</u>							
Fair, W.R.	124	21	5	5	6	5	--
*Corssen, G.	125	41	10	11	10	10	--
Hanno, P.M.	127	14	4	3	3	4	--
Lawson, R.K.	128	19	5	4	5	5	--
<u>Protocol 2238A - Gastroscopy without Meperidine Premedication</u>							
Lenze, F.L.	101	27	14	13	--	--	--
*Dunn, D.G.	110	41	20	21	--	--	--
Isenberg, J.I.	120	41	20	21	--	--	--
<u>Protocol 2239A - Gastroscopy with Meperidine Premedication</u>							
*White, P.F.	102	21	11	10	--	--	--
*Morissey, J.F.	104	20	10	10	--	--	--
<u>Protocol 2241A - Cardioversion without Meperidine Premedication</u>							
Lee, T.	109	5	1	4	--	--	--
<u>Protocol 2242A - Cardiac Catheterization with Meperidine Premedication</u>							
*Gensini, G.	114	22	10	12	--	--	--
*Hendrix, G.	115	20	10	10	--	--	--
*Lucbrook, P.A.	122	20	10	10	--	--	--
<u>Protocol 1032 - Cardiac Catheterization without Meperidine Premedication - Hemodynamic Study</u>							
*Fragen, R.	007 ⁹	30	10	10	--	--	10(?)
<u>Protocol 2243A - Angiography without Meperidine Premedication</u>							
*Lucbrook, P.A.	103	22	12	10	--	--	--
Ryan, T.J.	111	13	6	7	--	--	--

(1) 0.9% Saline
* Pivotal Study

Procedurally, all studies, with the exception of 009-Fragen, were similar. The test drug was administered slowly over a 2-3 minutes period until the sedative end point of slurred speech was reached. The time required to reach the end point and the dose of test drug administered were recorded. The study design was randomized, double-blind, parallel control.

Following the procedure, the physicians, who did not know which test drug had been administered, assessed the sedative properties of the test drugs.

One hour and 24 hours after the procedure, the endoscopic patients assessed the sedative - amnestic properties of the test drugs. In addition, in a questionnaire answered on the following day, endoscopic patients were asked whether they could recall events before, during and after the procedure.

The cardiovascular procedure studies did not utilize this questionnaire, nor did they evaluate the amnestic properties of the drugs. Furthermore, in the angiography study of Doctor Fragen, the patients did not evaluate sedation. His study was a special one which examined the cardiovascular effects of intravenous midazolam.

Recovery from sedation was measured by the Trieger Test in all studies except Doctor Fragen's. This test was completed by patients before medication and at one and two hours following completion of the endoscopy.

All adverse experiences were recorded and in all studies but Doctor Fragen's a follow-up examination was conducted for venous irritation or phlebitis.

The efficacy evaluations included results from 7 multicenter endoscopic protocols and 2 multicenter cardiovascular protocols (see Table 1). All studies under a protocol were included in the pooled efficacy results except for Dr. Ahmad's study (#112) under Protocol 2234A and Dr. Isenberg's study (#120) under Protocol 2238A. Dr. Ahmad's study was terminated after the enrollment of only four patients. The randomization code and sequential assignment of the test drugs was compromised in Dr. Isenberg's study since the drug shipment was divided incorrectly between two study sites. Due to the limited number of patients studied (one midazolam and four diazepam) the results of the cardioversion study (Dr. Lee, Protocol 2241A) were not included in the efficacy analyses.

There were two principal protocols for each endoscopic procedure. Protocols 2235A, 2237A, 2237B and 2239A allowed premedication with meperidine while no premedication was allowed in Protocols 2234A, 2236A and 2238A. The study results show that the mean end point of sedation (slurred speech was attained in from 2.8 to 4.8 minutes in the seven studies. The dose of midazolam was 27% less in premedicated patients; however, the induction time was 24% longer than in unpremedicated patients. There was a more narrow dose range when meperidine premedication was used.

The overall mean induction dose was 0.091 mg/kg in premedicated patients and the mean induction time was 4.1 minutes. In unpremedicated patients the mean induction dose was 0.116 mg/kg and the mean induction time was 3.3 minutes. In the endoscopy studies, for patients below age 40, the mean midazolam dose needed was 0.101 mg/kg compared with 0.118 mg/kg when meperidine was used as premedication. For patients over 59 years of age, the mean midazolam dose was 0.114 mg/kg compared with 0.084 mg/kg of midazolam when meperidine was used as premedication. There is a 26-27% lower requirement, therefore, in dose for patients over 59 compared with those less than 40 whether or not meperidine is used. Ten percent of midazolam patients (26 of 255) required an additional dose of the test drug to maintain sedation. Most patients requiring a maintenance dose were in bronchoscopy studies where some investigators had difficulty with the management of the patients since meperidine premedication was not allowed. In other instances, requirements for additional doses were due to the length of time required for completion of the procedure. Overall, in the cardiovascular studies, 35% of midazolam-treated patients (16 of 46) required additional doses to maintain sedation for completion of the procedure because of the extended length of angiographic and cardiac catheterization procedures.

The induction time was significantly shorter for midazolam-treated patients than for diazepam-treated patients. In the physicians' assessments of sedation about 5% or more of midazolam and diazepam-treated patients were evaluated as "good" or "excellent" for all parameters.

The midazolam-treated patients rated sedation as being significantly better than did those patients treated with diazepam on the one-hour questionnaire in two of seven multicenter studies (protocols 2234A and 2236A) and on the 24-hour questionnaire in two of seven multicenter studies (protocols 2235A and 2236A). Overall 90% of patients in both test and reference control groups answered affirmatively as to whether they were willing to undergo a future procedure the same way again. Overall, 208 of 256 (81.2%) midazolam-treated patients reported no pain compared with 160 of 261 (61.3%) diazepam-treated patients.

In the two multicenter cardiovascular studies (protocols 2242A and 2243A) midazolam treated patients rated quality of sedation as being significantly better than did diazepam-treated patients, one hour after the procedure. On the 24-hour assessment, quality of sedation was rated significantly better by midazolam-treated patients in only one of the two multicenter studies (protocol 2243A). There were no significant differences between treatment groups in the degree of pain associated with the procedure and in the number of patients who were willing to undergo a future procedure the same way again in the cardiovascular studies.

Midazolam-treated patients had no recall of the endoscope in 71.3% of cases (179 out of 251 midazolam-treated patients).

Safety

There were 29 studies in which 719 total patients received midazolam (320 patients), diazepam (326 patients) or placebo (73 patients). The safety evaluation of Dr. R. Fragen's study (009) will be revealed at the end of this section. Tables 2A and 2B lists all clinical adverse experiences and their incidence, grouped by body system. The significant adverse experiences will be discussed.

TABLE 2A

CLINICAL ADVERSE EXPERIENCES

	<u>MIDAZOLAM</u>		<u>DIAZEPAM</u>		<u>PLACEBO</u> <u>(MIDAZOLAM)</u>		<u>PLACEBO</u> <u>(DIAZEPAM)</u>	
	<u>No.</u> <u>Pts.</u>	<u>Per-</u> <u>cent</u>	<u>No.</u> <u>Pts.</u>	<u>Per-</u> <u>cent</u>	<u>No.</u> <u>Pts.</u>	<u>Per-</u> <u>cent</u>	<u>No.</u> <u>Pts.</u>	<u>Per-</u> <u>cent</u>
<u>CARDIOVASCULAR</u>								
Hypotension	4	1.3	2	0.6	-	-	-	-
Pulse Increased	104	32.5	106	32.5	2	5.4	6	16.7
Pulse Decreased	46	14.4	40	12.3	8	21.6	3	8.3
Map Decreased	93	29.1	58	17.8	2	5.4	4	11.1
Map Increased	27	8.4	37	11.3	3	8.1	4	11.1
Asystole	-	-	1	0.3	-	-	-	-
Myocardial Infarct	1	0.3	-	-	-	-	-	-
Bradycardia	1	0.3	-	-	-	-	-	-
Arrhythmia	-	-	1	0.3	-	-	-	-
<u>RESPIRATORY</u>								
Sore Throat	1	0.3	-	-	-	-	-	-
Coughing	1	0.3	-	-	-	-	-	-
Itching Nose	-	-	1	0.3	-	-	-	-
Laryngospasm	-	-	1	0.3	-	-	-	-
Laryngitis	1	0.3	-	-	-	-	-	-
Epiglottitis	1	0.3	-	-	-	-	-	-
Bronchospasm	1	0.3	-	-	-	-	-	-
Respiratory Depression	1	0.3	-	-	-	-	-	-
Apnea	5	1.6	5	1.5	-	-	-	-
Shallow Respirations	1	0.3	-	-	-	-	-	-
Airway Obstruction	1	0.3	-	-	-	-	-	-
Respiration Rate Increase	104	32.5	112	34.4	9	24.3	8	22.2
Respiration Rate Decrease	82	25.6	76	23.3	5	13.5	5	13.9
<u>LOCAL IV SITE</u>								
Phlebitis at injection site	-	-	2	0.6	-	-	-	-
Inflammation at injection site	-	-	1	0.3	-	-	-	-
Pain during injection of drug	1	0.3	5	1.5	-	-	-	-
Hematoma at IV site	-	-	1	0.3	-	-	-	-
Tenderness of vein	7	2.2	14	4.3	2	5.4	-	-
Redness of vein	7	2.2	5	1.5	-	-	-	-
Induration of vein	8	2.5	8	2.5	-	-	-	-

TABLE 28

CLINICAL ADVERSE EXPERIENCES

	MIDAZOLAM		DIAZEPAM		PLACEBO (MIDAZOLAM)		PLACEBO (DIAZEPAM)	
	No. Pts.	Per- cent	No. Pts.	Per- cent	No. Pts.	Per- cent	No. Pts.	Per- cent
<u>CNS AND RELATED</u>								
Excessive Sedation	3	0.9	1	0.3	-	-	-	-
Deep Sedation	2	0.6	-	-	-	-	-	-
Unresponsive	1	0.3	-	-	-	-	-	-
Drowsy	3	0.9	1	0.3	-	-	-	-
Lethargy	1	0.3	-	-	-	-	-	-
Weak	1	0.3	1	0.3	-	-	-	-
Confusion	2	0.6	-	-	-	-	-	-
Amnesia (Retrograde)	1	0.3	-	-	-	-	-	-
Anxiety	1	0.3	-	-	-	-	-	-
Agitated	-	-	1	0.3	-	-	-	-
Argumentative	1	0.3	-	-	-	-	-	-
Headache	4	1.3	5	1.5	-	-	-	-
Clenching of Jaws	1	0.3	-	-	-	-	-	-
Dizziness	1	0.3	1	0.3	1	2.7	1	2.8
<u>GASTROINTESTINAL</u>								
Dry mouth	1	0.3	-	-	1	2.7	-	-
Taste acid	1	0.3	-	-	-	-	-	-
Throat pain	-	-	1	0.3	-	-	-	-
Nausea	4	1.3	5	1.5	-	-	-	-
Vomiting	3	0.9	3	0.9	-	-	-	-
<u>MISCELLANEOUS</u>								
Hiccoughs	1	0.3	-	-	-	-	-	-
Apathy	-	-	1	0.3	-	-	-	-
Chest pain	1	0.3	1	0.3	-	-	-	-
Rash legs	-	-	1	0.3	-	-	-	-
Swollen armpit	-	-	1	0.3	-	-	-	-
Phlebitis (Other than local IV site)	-	-	2	0.6	-	-	-	-
Blood loss	1	0.3	-	-	-	-	-	-
Blurred vision	1	0.3	-	-	-	-	-	-
Conjunctivitis	-	-	1	0.3	-	-	-	-
Tinnitus	-	-	1	0.3	-	-	-	-
<u>NUMBER OF PATIENTS TREATED</u>	320	-	326	-	37	-	36	-

Clinically Significant Hypotension

Four midazolam and two diazepam-treated patients developed clinically significant hypotension. The majority of these patients also received meperidine in addition to the test drug. Where both agents were used it was felt that the combined effects of both meperidine and the benzodiazepine may have contributed to the development of these reactions.

Table 3

<u>Clinically Significant Hypotension</u>				
<u>Study and No. EDP #</u>	<u>Age (yrs)</u>	<u>Test Drug</u>	<u>Adjuvant Therapy</u>	<u>Comments</u>
102/5	65	Midazolam 0.100 mg/kg	Meperidine 1.0 mg/kg Local Anesthetic	- Investigator treated this with Narcan®.
107/4	60	Midazolam 0.091 mg/kg	Meperidine 0.909 mg/kg Local Anesthetic	- Investigator treated this with dopamine.
112/2	54	Midazolam 0.181 mg/kg	Local Anesthetic	- Spontaneous recovery No treatment required.
117/13	72	Midazolam 0.095 mg/kg	Meperidine 1.3 mg/kg Local Anesthetic	- The patient also had apnea which Invest- igator treated with Narcan®.
125/9	61	Diazepam 0.142 mg/kg	Local Anesthetic	- Spontaneous recovery No treatment required.
137/11	67	Diazepam 0.066 mg/kg	Meperidine 0.676 mg/kg Local Anesthetic	- Spontaneous recovery No treatment required.

Clinically Significant Respiratory Depression and/or Apnea

Five midazolam and five diazepam-treated patients developed apnea. Two midazolam-treated patients required corrective measures and had their bronchoscopies cancelled. All other patients recovered spontaneously. Both midazolam-treated patients received meperidine. Two additional midazolam-treated patients (study 112, patient _____ and study 113, patient _____) had minor transient respiratory difficulty; however, they underwent their endoscopic procedures and had no significant sequelae.

TABLE 4

Study and Pt. EDP #	Age (yrs.)	Apnea		
		Test Drug	Adjuvant Therapy	Comments
107/12	50	Midazolam 0.083 mg/kg	Meperidine 0.833 mg/kg and Local Anesthetic	- Patient was treated with Narcan® and breathing resumed spontaneously.
109/1	30	Midazolam 0.136 mg/kg	-----	- Spontaneous recovery. No treatment required.
111/9	61	Midazolam 0.068 mg/kg	Local Anesthetic	- Spontaneous recovery. No treatment required.
117/13	72	Midazolam 0.095 mg/kg	Meperidine 1.3 mg/kg IM and Local Anesthetic	- Patient was treated with Narcan®
150/19	79	Midazolam 0.161 mg/kg	* Local Anesthetic	- Spontaneous recovery. No treatment required.
109/2	57	Diazepam 0.101 mg/kg	-----	- Spontaneous recovery. No treatment required.
117/1	56	Diazepam 0.072 mg/kg	Meperidine 0.575 mg/kg and Local Anesthetic	- Spontaneous recovery. No treatment required.
150/9	76	Diazepam 0.259 mg/kg	Local Anesthetic	- Spontaneous recovery. No treatment required.
150/14	66	Diazepam 0.219 mg/kg	Local Anesthetic	- Spontaneous recovery. No treatment required.
150/12	69	Diazepam 0.286 mg/kg	Local Anesthetic	- Spontaneous recovery. No treatment required.

Central Nervous System and Related Side Effects

Three elderly midazolam-treated patients experienced excessive sedation and two others experienced deep sedation. Another became unresponsive to painful stimuli and required treatment with Narcan. All of the above patients, except one, received meperidine as premedication and the investigators felt that the combined drug sedative effects produced excessive sedation.

TABLE 5

CNS and Related Side Effects

<u>Adverse Experience</u>	<u>Study and Pt. EDP #</u>	<u>Age (yrs)</u>	<u>Test Drug</u>	<u>Adjuvant Therapy</u>	<u>Comments</u>
Deep Sedation and Hypotension	107/4	60	Midazolam 0.091 mg/kg	Meperidine 0.909 mg/kg	-Pt. also developed hypotension which was reversed by dopamine.
Deep Sedation and Apnea	107/12	50	Midazolam 0.083 mg/kg	Meperidine 0.833 mg/kg	-Pt. also had transient apnea and he received Narcan® and breathing resumed spontaneously.
Excessive Sedation	105/16	69	Midazolam 0.134 mg/kg	—	-One hour after the procedure patient could be aroused only with painful stimuli. No specific treatment required.
Excessive Sedation	125/29	96	Midazolam 0.083 mg/kg	Meperidine 0.833 mg/kg	-Alzheimer's disease.
Excessive Sedation	128/7	82	Midazolam 0.057 mg/kg	Meperidine 1.14 mg/kg	-No specific treatment required.
Excessive Sedation	128/5	78	Diazepam 0.016 mg/kg	Meperidine 0.77 mg/kg	-Excessive sedation following meperidine injection therefore test drug dose was reduced.
Unresponsiveness	124/12	65	Midazolam 0.152 mg/kg	Meperidine 0.759 mg/kg	Narcan® was given to reverse the effects.

Three midazolam-treated patients (study #101, patient _____, study #101, patient _____, study 110, patient _____) and one diazepam-treated patient (study 101, patient _____) experienced drowsiness following the study, but none of them required any specific corrective measures. Patient _____ of study 111 (midazolam) experienced a transient period of confusion, anxiety and retrograde amnesia for about one hour, with spontaneous recovery. Assuming the correct dose of meperidine to be about 1 mg/kg, then all of the premedicated patients in table 5 got correct doses except for patients _____ of study 128, who was slightly over. The mean dose of midazolam overall was 0.161 mg/kg for patients over 59 which was reduced to 0.113 mg/kg when premedicated with meperidine. There were four midazolam-treated patients who were premedicated and were over 59. Of these two got a dose greater than the mean and two got less than the mean dose, for premedicated patients. Additionally, the one premedicated 50 year old patient clearly got a lower dose of midazolam than would be anticipated for the age. Therefore lowering of the dose of midazolam may not provide complete freedom from excessive sedation in patients who have had concomitant narcotics.

Patient _____ of study 117 (midazolam) experienced clenching of the jaws twice during the administration of a local anesthetic to the pharynx and once immediately following the injection of midazolam. This lasted only 1-2 minutes and the patient underwent the subsequent procedure uneventfully. According to the investigator, this was not related to the test drug, since the clenching of the jaws was observed prior to the injection of midazolam.

Other CNS and related side effects were minor, transient and did not require any specific corrective measures.

Local Side Effects at the Intravenous Site

Table 6 suggests that midazolam produces less pain during injection and less irritation at the intravenous site.

Gastrointestinal Side Effects

As seen in Table 2B, minor transient side effects such as nausea and vomiting were seen with almost equal frequency in both midazolam and diazepam-treated patients.

Other Side Effects

Patient _____ of Study 123 (midazolam) had mild hiccoughs, which subsided spontaneously after 15-30 seconds. Another midazolam-treated patient (study 121, _____) experienced pharyngeal bleeding and bronchospasm which forced the cancellation of the bronchoscopy. According to the investigator, this had no relation to the test drug administration and resulted from a pre-existing condition.

Patient of study 107 was found to have epiglottitis and laryngitis during the examination immediately prior to the bronchoscopy; therefore, the investigator cancelled the procedure.

Changes in Vital Signs

The changes in vital signs of 20% from baseline are included in Table 2A under the headings of respiratory and cardiovascular adverse experiences. Changes in respiratory rate, pulse rate and mean arterial pressure were the most common adverse experiences. The majority of these changes were transient and clinically insignificant. Tables 7A, 7B and 7C summarize these changes by the phase of the study and severity of these changes. Most changes did not require any specific treatment and had no significant clinical implication. During induction, changes were for the most part, comparable between the two test drug groups. Clinically significant hypotension and apnea has already been commented on.

TABLE 6

Local Side Effects at the Intravenous Site

	<u>Midazolam</u>		<u>Diazepam</u>	
	<u>No.</u>	<u>Per-</u>	<u>No.</u>	<u>Per-</u>
	<u>Pts.</u>	<u>cent</u>	<u>Pts.</u>	<u>cent</u>
Number of Patients treated	320		326	-
Phlebitis at site of injection	-	-	2	0.6
Inflammation of injection site	-	-	1	0.3
Pain during injection of study drug	1	0.3	5	1.3
Hematoma at IV site	-	-	1	0.3
Tenderness of vein	7	2.2	14	4.3
Redness of vein	7	2.2	5	1.5
Induration of vein	8	2.5	8	2.5

TABLE 7A

CHANGES IN RESPIRATORY RATE

	<u>MIDAZOLAM</u>		<u>DIAZEPAM</u>		<u>PLACEBO</u> <u>(MIDAZOLAM)</u>		<u>PLACEBO</u> <u>(DIAZEPAM)</u>	
	<u>No.</u>	<u>Per-</u> <u>Pts. cent</u>	<u>No.</u>	<u>Per-</u> <u>Pts. cent</u>	<u>No.</u>	<u>Per-</u> <u>Pts. cent</u>	<u>No.</u>	<u>Per-</u> <u>Pts. cent</u>
<u>NUMBER OF PATIENTS TREATED</u>	320	-	326	-	37	-	36	-
<u>DURING INDUCTION</u>								
Increase (20-30%)	4	1.3	7	2.1	1	2.7	-	-
Increase (30-50%)	-	-	5	1.5	-	-	-	-
Increase (>50%)	-	-	1	0.3	-	-	-	-
Decrease (20-30%)	14	4.4	13	4.0	-	-	-	-
Decrease (30-50%)	1	0.3	3	0.9	-	-	-	-
Decrease (>50%)	1	0.3	-	-	-	-	-	-
<u>DURING MAINTENANCE</u>								
Increase (20-30%)	39	12.2	51	15.6	4	10.8	4	11.1
Increase (30-50%)	20	6.3	23	7.1	1	2.7	-	-
Increase (>50%)	17	5.3	13	4.0	-	-	-	-
Decrease (20-30%)	40	12.5	41	12.6	2	5.4	3	8.3
Decrease (30-50%)	11	3.4	11	3.4	-	-	-	-
Decrease (>50%)	6	1.9	3	0.9	-	-	-	-
<u>DURING RECOVERY</u>								
Increase (20-30%)	24	7.5	31	9.5	3	8.1	5	13.9
Increase (30-50%)	14	4.4	17	5.2	2	5.4	1	2.8
Increase (>50%)	18	5.6	16	4.9	-	-	-	-
Decrease (20-30%)	34	10.6	24	7.4	3	8.1	2	5.6
Decrease (30-50%)	12	3.8	16	4.9	2	5.4	-	-
Decrease (>50%)	1	0.3	12	0.6	-	-	-	-
Ranges include >lower limit and <upper limit								

TABLE 7B

CHANGES IN PULSE RATE

	<u>MIDAZOLAM</u>		<u>DIAZEPAM</u>		<u>PLACEBO (MIDAZOLAM)</u>		<u>PLACEBO (DIAZEPAM)</u>	
	<u>No.</u>	<u>Per- Pts. cent.</u>	<u>No.</u>	<u>Per- Pts. cent.</u>	<u>No.</u>	<u>Per- Pts. cent.</u>	<u>No.</u>	<u>Per- Pts. cent.</u>
<u>NUMBER OF PATIENTS TREATED</u>	320	-	320	-	37	-	36	-
<u>DURING INDUCTION</u>								
Increase (20-30%)	7	2.2	9	2.8	-	-	-	-
Increase (30-50%)	2	0.6	4	1.2	-	-	-	-
Increase (>50%)	-	-	1	0.3	-	-	-	-
Decrease (20-30%)	2	0.6	2	0.6	-	-	-	-
Decrease (30-50%)	1	0.3	-	-	-	-	-	-
Decrease (>50%)	-	-	-	-	-	-	-	-
<u>DURING MAINTENANCE</u>								
Increase (20-30%)	35	10.9	33	10.1	1	2.7	3	8.3
Increase (30-50%)	33	10.3	38	11.7	-	-	1	2.8
Increase (>50%)	22	6.9	19	5.8	-	-	-	-
Decrease (20-30%)	12	3.8	9	2.8	1	2.7	2	5.6
Decrease (30-50%)	5	1.6	4	1.2	-	-	-	-
Decrease (>50%)	1	0.3	-	-	-	-	-	-
<u>DURING RECOVERY</u>								
Increase (20-30%)	24	7.5	28	8.6	1	2.7	2	5.6
Increase (30-50%)	18	5.6	22	6.7	-	-	1	2.8
Increase (>50%)	13	4.1	7	2.1	-	-	-	-
Decrease (20-30%)	29	9.1	27	8.3	8	21.6	2	5.6
Decrease (30-50%)	7	2.2	5	1.5	-	-	-	-
Decrease (>50%)	-	-	1	0.3	-	-	-	-
Ranges include >lower limit and <upper limit								

Fragen Study (009)

In the Fragen study there were no significant differences in hemodynamic parameters, between the two test drug groups and dynamics were only minimally altered.

TABLE 7C

CHANGES IN MEAN ARTERIAL PRESSURE

	<u>MIDAZOLAM</u>		<u>DIAZEPAM</u>		<u>PLACEBO</u> <u>(MIDAZOLAM)</u>		<u>PLACEBO</u> <u>(DIAZEPAM)</u>	
	<u>No.</u> <u>Pts.</u>	<u>Per-</u> <u>cent</u>	<u>No.</u> <u>Pts.</u>	<u>Per-</u> <u>cent</u>	<u>No.</u> <u>Pts.</u>	<u>Per-</u> <u>cent</u>	<u>No.</u> <u>Pts.</u>	<u>Per-</u> <u>cent</u>
<u>NUMBER OF PATIENTS TREATED</u>	320	-	326	-	37	-	36	-
<u>DURING INDUCTION</u>								
Increase (20-30%)	2	0.6	1	0.3	-	-	-	-
Increase (30-50%)	1	0.3	-	-	-	-	-	-
Increase (>50%)	-	-	-	-	-	-	-	-
Decrease (20-30%)	7	2.2	3	0.9	1	2.7	-	-
Decrease (30-50%)	1	0.3	2	0.6	-	-	-	-
Decrease (>50%)	-	-	-	-	-	-	-	-
<u>DURING MAINTENANCE</u>								
Increase (20-30%)	11	3.4	20	6.1	2	5.4	2	5.6
Increase (30-50%)	8	2.5	11	3.4	1	2.7	-	-
Increase (>50%)	2	0.6	-	-	-	-	2	5.6
Decrease (20-30%)	34	10.6	22	6.7	-	-	-	-
Decrease (30-50%)	15	4.7	6	1.8	-	-	1	2.8
Decrease (>50%)	-	-	-	-	-	-	-	-
<u>DURING RECOVERY</u>								
Increase (20-30%)	6	1.9	9	2.8	-	-	1	2.8
Increase (30-50%)	2	0.6	2	0.6	-	-	-	-
Increase (>50%)	1	0.3	1	0.3	-	-	1	2.8
Decrease (20-30%)	51	15.9	36	11.0	1	2.7	3	8.3
Decrease (30-50%)	17	5.3	7	2.1	-	-	-	-
Decrease (>50%)	-	-	-	-	-	-	-	-

Ranges include >lower limit and <upper limit

Package Insert

Only sections applicable to the studies of sedation for endoscopies and short procedures will be commented on here.

Description

Not applicable.

Clinical Pharmacology

The statement: "When used intravenously as a sedative for endoscopic or other short therapeutic or diagnostic procedures, the end point of slurred speech can be attained within 2.8 to 4.8 minutes, depending on the total dose administered and whether or not preceded by narcotic premedication." is correct but requires elaboration to prevent a misleading inference. The induction time range is inclusive of all the mean times in all the pooled endoscopic or short procedural studies with the exception of Fragen's cardiovascular hemodynamic study and Lee's aborted cardioversion study, including premedication with meperidine and procedures not using meperidine premedication. While the mean induction time was dependent on the total dose administered and whether or not preceded by narcotic premedication, the relationships of induction time to these two factors are opposite. In general, when meperidine was used as a premedicant, the dose of midazolam required for sedation was less than the dose of midazolam required by patients who did not receive premedication. It also followed that while the dose was less in the premedicated patients, generally (with the exception of cystoscopy), the induction time was longer than in unpremedicated patients (See Table I). The mean age and weights in corresponding types of pooled studies with and without meperidine premedication are comparable; therefore, the only variables which relate to mean induction time are dose of midazolam and use of meperidine.

TABLE I

Mean Induction Time Related to Mean Dose
of Midazolam in Pooled Studies

<u>Protocol No.</u>	<u>Pooled Study</u>	<u>Premedication With Meperidine</u>	<u>Mean Age (range)</u>	<u>Mean Wt.(kg) (range)</u>	<u>Mean Dose (mg/kg)</u>	<u>Mean Ind. Time (min.)</u>
2236A	Cystoscopy	No	52.2 (17-86)	71.4 (45-157)	.152	3.9
2243A	Angiography	No	52.4 (28-62)	85.7 (58-115)	.121	3.5
2238A	Gastroscopy	No	49.1 (19-73)	72.8 (46-115)	.164	2.8
2234A	Bronchoscopy	No	54.8 (21-85)	71.5 (50-113)	.110	3.0
2337A	Cystoscopy	Yes	52.4 (28-88)	70.7 (53-94)	.090	2.9
2237B	Cystoscopy	Yes	60.0 (18-96)	72.3 (44-114)	.104	4.2
2242A	Cardiac Catheterization	Yes	53.8 (31-68)	75.2 (52-103)	.072	4.83
2239A	Gastroscopy	Yes	50.5 (20-76)	69.2 (44-132)	.095	4.3
2235A	Bronchoscopy	Yes	49.8 (25-72)	69.8 (41-123)	.094	4.4

This relationship of induction time to premedication is not apparent from the phrase ". . . depending on the total dose administered and whether or not preceded by narcotic premedication"; and it would be appropriate to augment this phrase with an additional statement clarifying the fact that premedicated patients required lower induction doses but had longer induction times than unpremedicated patients.

Indications

In the last sentence of this section it states that "Seventy-three percent of the patients in the endoscopy studies had no recall of introduction of the scope." This should be 71% (179/251).

The indication "for conscious sedation prior to short surgical, diagnostic, therapeutic or endoscopic procedures, such as bronchoscopy, gastroscopy, cystoscopy, urinary angiography and cardiac catheterization, either alone or in conjunction with a narcotic" should be modified since the actual studies included only diagnostic, endoscopic or cardiovascular procedures. Therefore,

the words "short surgical" and "therapeutic" should be deleted. We do not know how patients would respond under the pain and stress of conscious surgical and therapeutic interventions.

Contraindications: Not Applicable.

Warnings: Adequate.

Precautions: Adequate.

Adverse Reactions

To the list of reactions, hypotension should be added, especially when premedicated with narcotic. This occurred in four cases, three of which were premedicated with meperidine (study 102, study 107, study 117, and one of which was not premedicated with meperidine (study 112,

Dosage and Administration

The paragraph entitled "INTRAVENOUSLY Endoscopic or Cardiovascular Procedures" requires some elaboration. In the right hand column it states "Generally 0.1 to 0.15 mg/kg is adequate, but up to 0.2 mg/kg may be given, particularly when concomitant narcotics are omitted." An additional statement should be added to the effect that when a dose of 0.15 mg/kg is exceeded there is an increased frequency of depressed respiration and drowsiness. (See Table 2).

TABLE 2

Dose Related Adverse Reactions
When Concomitant Meperidine Was Not Given

<u>Induction dose (mg/kg)</u>	<u>Study #</u>	<u>Patient #</u>	<u>Reaction</u>
<u>Induction dose 0.15 mg/kg</u>			
0.217	101		lethargic, weak, dizzy
0.203	101		drowsiness following study
0.206	101		drowsiness following study
0.181	112		respiratory depression and hypotension
0.169	113		shallow respirations
0.161	150		apnea following induction
<u>Induction dose 0.15 mg/kg</u>			
0.134	105		excessive sedation after procedure
0.144	111		confusion
0.068	111		apnea

How Supplied: Not Applicable.

Conclusions

Effectiveness

1. The nine pooled studies are adequate and well-controlled as are the pivotal individual studies listed by the sponsor (see Table 1 in previous efficacy evaluation).
2. When used intravenously as a sedative for endoscopic or diagnostic procedures midazolam was as effective as was diazepam and the end point of sedation was more rapid following administration of midazolam than diazepam at comparable doses.
3. The end point of slurred speech was attained in the pooled endoscopic and diagnostic studies within mean times of 2.8 to 4.8 minutes.
4. The induction time depends on the total dose of midazolam.
5. The induction time also depends on whether induction is preceded by narcotic premedication, and in general the induction doses were smaller, but the induction times were longer when narcotic premedication was used.
6. In general, the desired end point of slurred speech was attained with a dose of less than 0.150 mg/kg of midazolam without narcotic premedication and the dose was proportionately less when meperidine premedication was used.
7. Midazolam was as effective as diazepam in producing a relaxed and cooperative patient as assessed by the physician.
8. Patients tended to rate the quality of sedation as better with midazolam and experienced less pain during the procedure than those patients who received diazepam.
9. Seventy one percent of the patients in the endoscopy studies had no recall of introduction of the scope, indicating effectiveness in inducing failure of recall of the procedure.

Safety

1. The majority of adverse experiences, as defined by the sponsor were changes in vital signs greater than 20% from baseline. Most of these were transient and of no clinical significance.
2. Midazolam, in the doses used, was as safe as diazepam in providing sedation during endoscopic and cardiovascular procedures, both with and without meperidine premedication.

3. In doses above 0.15 mg/kg there was an increased frequency of depressed respiration and drowsiness.
4. Clinically significant adverse experiences which occurred were:
 - a. Hypotension (especially with meperidine premedication)
 - b. Apnea
 - c. Respiratory depression
 - d. Shallow respiration
 - e. Excessive sedation
 - f. -Deep sedation
 - g. Unresponsiveness
 - n. Tenderness of vein - IV site
 - i. Redness of vein - IV site
 - j. Induration of vein - IV site

Recommendations

The use of midazolam for endoscopic and short diagnostic procedures is medically approvable. The draft package insert should be corrected as follows in a written communication to the sponsor:

1. Clinical Pharmacology

In the third paragraph of this section in the second sentence delete "other short therapeutic" since no intravenous sedative studies were conducted in therapeutic procedures, only diagnostic ones.

2. Clinical Pharmacology

The relationship of induction time to narcotic premedication is not apparent in the second sentence of the third paragraph in the phrase "depending on the total dose administered and whether or not preceded by narcotic premedication." An additional sentence should be added which states: "Premedicated patients required lower induction doses but had longer induction times than unpremedicated patients."

3. Indications

The indication "intravenously as an agent for conscious sedation prior to short surgical, diagnostic, therapeutic or endoscopic procedures, ..." should have the words "surgical" and "therapeutic" deleted, since no studies of these types of procedures were conducted and we do not know how patients would respond under the pain and stress of conscious surgical and therapeutic interventions.

4. In the last sentence of this section it states that "seventy-three percent of the patients in the endoscopy studies had no recall of introduction of the scope." This figure should be changed to seventy-one percent, since it represents 179 out of 251 patients.

5. Adverse Reactions

To the list of adverse reactions following intravenous administration add "hypotension, particularly when premedicated with a narcotic."

6. Dosage and Administration

In the subsection entitled "INTRAVENOUSLY Endoscopic or Cardiovascular Procedures," in the right hand column it states "generally 0.1 to 0.15 mg/kg is adequate, but up to 0.2 mg/kg may be given, particularly when concomitant narcotics are omitted." An additional statement should be added which states: "When a dose of 0.15 mg/kg is exceeded there is an increased frequency of depressed respiration and drowsiness."

Harvey Dickstein
Harvey Dickstein, M.D.

NDA 18-654

HFN-160

HFN-120

HFN-340

R/D HLDickstein 4/18/84

R/D Init. by PGWalters 4/18/84

FT OLA, JB, TD, KR W 1513N, 2478P, 1553N, 1559N, 1561N, 1564N, 1568N, 1570N,

1571N, 1574N, Archives 0084N and 0088N

Doc. Room 160

NDA

18654

Chem

Rev

CHEMIST'S REVIEW (If necessary, continue any item on 8 1/2" x 10 1/2" paper. Key continuation to item by number.)		1. ORGANIZATION HFN-120	2. NDA NUMBER 18-654
3. NAME AND ADDRESS OF APPLICANT (City and State) Hoffman-LaRoche Nutley, New Jersey 07110		4. AF NUMBER	
		5. SUPPLEMENT (S) NUMBER(S) DATE(S)	
6. NAME OF DRUG Versed	7. NONPROPRIETARY NAME Midazolam		
8. SUPPLEMENT(S) PROVIDES FOR: Alternate manufacturing site		9. AMENDMENTS AND OTHER (Reports, etc.) DATES 11-14-84	
10. PHARMACOLOGICAL CATEGORY Anesthetic	11. HOW DISPENSED ☒ RX ☐ OTC	12. RELATED IND/NDA/DMF(S)	
13. DOSEAGE FORM (S) Unit dose vials	14. POTENCY (ies)		
15. CHEMICAL NAME AND STRUCTURE		16. RECORDS AND REPORTS CURRENT ☐ YES ☐ NO REVIEWED ☐ YES ☐ NO	
17. COMMENTS Alternate manufacturing site:			
18. CONCLUSIONS AND RECOMMENDATIONS Approval from the Standi... Point of Manufacturing Controls recommended pending approval of the NDA.			
19. REVIEWER			
NAME V. Iliev	SIGNATURE <i>V. Iliev</i>	DATE COMPLETED 2-7-85	

NYK-DO

NDA 18-654
HFN-120
HFN-120/V.Iliev
Init. R.Shultz/2-8-85

Orig. NDA 18-654, NDK-DO, HFN 616, HFN 120, HFN 120/Viliev/2/7/84, RD/init:RShultz/2/7/84, FT/AK/2/7/84

CHEMIST'S REVIEW (If necessary, continue any item on 8" x 10" paper. For continuation to item by number.)		1. ORGANIZATION HFN 120	2. NDA NUMBER 18-654
3. NAME AND ADDRESS OF APPLICANT (City and State) Hoffmann La Roche Nutley, New Jersey 07110		4. AP NUMBER	
5. NAME OF DRUG Midazolam		6. SUPPLEMENT (S) NUMBER(S) DATE(S)	
7. NONPROPRIETARY NAME		8. AMENDMENTS AND OTHER (Reports, etc) DATES Feb. 3, 1984	
9. SUPPLEMENT(S) PROVIDES FOR: Repeat analysis method validation		10. PHARMACOLOGICAL CATEGORY Anesthetic	
11. HOW DISPENSED ☒ RX ☐ OTC		12. RELATED IND/NDA/DMF(S)	
13. DOSAGE FORM (S) Injectable	14. POTENCY (log)		
15. CHEMICAL NAME AND STRUCTURE		16. RECORDS AND REPORTS CURRENT ☐ YES ☐ NO REVIEWED ☐ YES ☐ NO	
17. COMMENTS The method found to be suitable for regulatory purposes. However, the analyst feels that the method would be improved if the			
18. CONCLUSIONS AND RECOMMENDATION(S) Approval Recommended with letter			
19. NAME V. Iliev		SIGNATURE <i>V. Iliev</i>	DATE COMPLETED February 7, 1984
DISTRIBUTION ☐ ORIGINAL JACKET ☐ REVIEWER ☐ DIVISION FILE			

Orig. NDA 18-654, NDK-DO, HFN 616, HFN 120, HFN 120/Viliev/10/25/83, RD/init:RShultz/10/25/83, FT/AAK/10/26/83

CHEMIST'S REVIEW (If necessary, continue any item on 8" x 10 1/2" paper. Key continuation to item by number.)		1. ORGANIZATION HFN 120	2. NDA NUMBER 18-654
3. NAME AND ADDRESS OF APPLICANT (City and State) Hoffman-La Roche Inc. Nutley, New Jersey 07110		4. AF NUMBER	
6. NAME OF DRUG Midazolam		7. NONPROPRIETARY NAME	
8. SUPPLEMENT(S) PROVIDES FOR: Validation report		3. SUPPLEMENT(S) NUMBER(S) DATE(S)	
10. PHARMACOLOGICAL CATEGORY Anesthetic		11. HOW DISPENSED ☒ RX ☐ OTC	
13. DOSAGE FORM (S) Injectable		14. POTENCY (See)	
15. CHEMICAL NAME AND STRUCTURE		12. RELATED IND/NDA/DMF(S)	
		9. AMENDMENTS AND OTHER (Reports, etc) DATES October 11, 1983	
		16. RECORDS AND REPORTS CURRENT ☐ YES ☐ NO REVIEWED ☐ YES ☐ NO	
17. COMMENTS			
18. CONCLUSIONS AND RECOMMENDATIONS Approval recommended, satisfactory from standpoint of controls with letter			
19. NAME V. Iliev		REVIEWER SIGNATURE <i>V. Iliev</i>	
		DATE COMPLETED 10/25/83	
DISTRIBUTION		☐ ORIGINAL JACKET ☐ REVIEWER ☐ DIVISION FILE	

CHEMIST'S REVIEW

1. ORGANIZATION

2. NDA NUMBER

HFN-120

18-654

3. NAME AND ADDRESS OF APPLICANT (CITY AND STATE)

Hoffmann-La Roche Inc.
Nutley, NJ 07110

4. AF NUMBER

5. SUPPLEMENT(S)
NUMBER(S) DATES(S)

6. NAME OF DRUG

Versed

7. NONPROPRIETARY NAME

mifazolam

8. REC'D. BY CHEMIST:

6/6/85

9. SUPPLEMENT(S) PROVIDES FOR:

New manufacturing facility

10. AMENDMENTS AND OTHER
(REPORTS, ETC.) DATES

5/28/85

11. PHARMACOLOGICAL CATEGORY

Hypnotic

12. HOW DISPENSED

xx (RX) (OTC)

13. RELATED IND/NDA/DMF(S)

14. DOSAGE FORM(S)

Parenteral

15. POTENCY(IES)

16. CHEMICAL NAME AND STRUCTURE

17. RECORDS AND REPORTS

CURRENT		
YES	_____	NO
REVIEWED		
YES	_____	NO

18. COMMENTS

19. CONCLUSIONS AND RECOMMENDATIONS

Satisfactory from stand point of controls.
Acknowledge/Retain letter recommended.

20.

REVIEWER

NAME

SIGNATURE

DATE COMPLETED

Venelin Iliev, Ph.D.

V. Iliev

6/6/85

Copies:

ORIG:NDA

HFN-120

HFN-120/Viliev/6/6/85

INIT:RCSultz/6/6/85

ft/evh/6/7/85

DOC#00920

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

Chemist's Review # 1
Date 4-1-83

A. 1. NDA/IND # 18-65A

Applicant/Sponsor: Hoffmann-La Roche
Address: 340 Kingsland Street, Nutley, New Jersey 07110
AF #

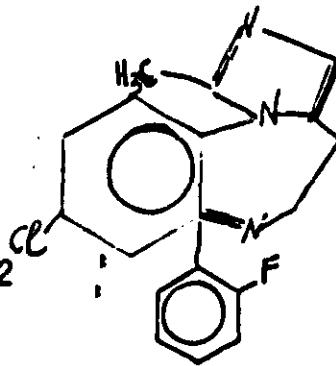
2. Product Name(s): Midazolam
Proprietary:
Non-proprietary:
USAN:
Compendium:
Code Name and/or number:

3. Dosage Form(s) and Route(s) of Administration: Injectable
Rx/OTC

4. Pharmacological Category and/or Principal Indication: anesthesia

5. Structural Formula and Chemical Name(s):

8-chloro-6-(2-fluorophenyl)-
Methyl 4 H midazo [1,5a]
1,4 benzodiazepine



B. 1. Initial Submission: Dec. 15, 1982

2. Amendments:

3. Supporting IND, NDA, MF, and Letters of Authorization:

4. Related Documents (INDs, NDAs, etc.):

C. Remarks:

D. Conclusions and/or Recommendations:

Satisfactory from the standpoint of controls pending satisfactory validation of the methodology.

CC:
NDA Orig.
HFN-120 ✓
HFN-120/Viliev/4/1/83
RDinit. RCSultz/4/1/83/FT/lca/4/1/83

V. Viliev
Venelin Viliev, Ph.D.

Reviewing Chemist

NDA

18654

Clinical

Data

160

15

NDA 18-654

Date Completed: 27 June 1984

Review and Evaluation of Clinical Data
(Medical Officer's Consultative Review of Original NDA Submission)

Regulating Division: Division of Neuropharmacological Drug Products HFN-120

Sponsor: Roche, Nutley, N. J.

Name of Product: Versed (midazolam) Injection

Category: Benzodiazepine, First water soluble benzodiazepine tested.

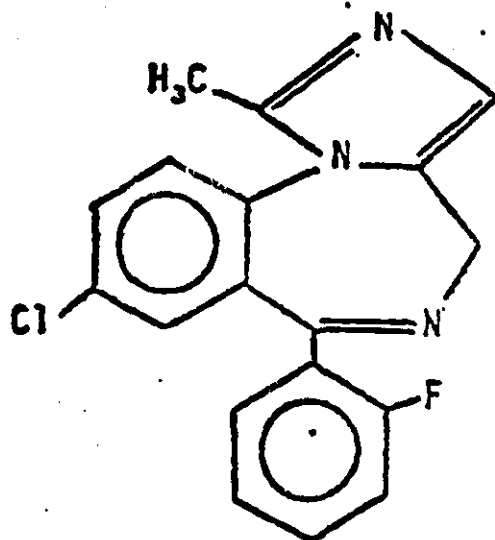
Formulation: Each ml of aqueous solution contains the equivalent of 5 mg midazolam, made soluble by pH adjustment to 3 with hydrochloric acid (and, if necessary, sodium hydroxide). This is sometimes referred to as midazolam hydrochloride. Ingredients & preservatives include 0.8% sodium chloride, 0.01% disodium edetate and 1% benzyl alcohol. Versed is supplied in ampuls &/or vials of 1 ml, 2 ml, 5 ml and 10 ml, as well as 1 and 2 ml "Tel-E-Ject^R" disposable syringes.

Many of the early studies involve midazolam maleate, the first aqueous solution to be tested. This solution is clinically equivalent to the current hydrochloride solution (see Protocol No. 2212A, H. Bivens & J. Mahaffey).

Date of Submission: 15 December 1982.

Use: This summary is concerned with intramuscular use for pre-anesthetic medication for the purpose of producing sedation and with intravenous use for induction of general anesthesia. This application is also concerned with intravenous use to facilitate endoscopies and with intramuscular use for pre-anesthetic medication for the purpose of managing situational anxiety; the first of these claims has been reviewed by Harvey Dickstein, M. D., Acting Group leader (see review dated 11 April 1984) and the second is under review by the Staff of HFN-120 (H. Lee, Ph. D.)

Structural Formulae:



SPECIAL NOTE: This review is concerned with an unusually large number of studies. Please read the **CONCLUSIONS AND RECOMMENDATION** Sections, conveniently placed first, before checking the Index (placed after a review of the package insert) to determine what else to read. The **CONCLUSIONS** Section makes frequent reference to individual studies judged worthy of supporting Conclusions. Some studies are cited more than once.

Index starts on page 28.

CONCLUSIONS:

I. Intravenous Dosage: The wide range of intravenous inductions doses tested can lead to confusion unless the reasons for this are understood. This will be discussed first because all other decisions about whether to accept or reject my recommendations should be simple by comparison. Many studies, particularly early studies, involve the administration of low doses followed by a 2 minute wait. If the patient was not asleep in 2 minutes, 25% of the initial dose was repeated and this was continued every 2 minutes until anesthesia was induced. Mean induction times were often acceptable, within 2 minutes, but the range was extreme, including cases requiring over 600 seconds for induction. In addition, clinical experience with thiopental (the standard induction agent, accounting for perhaps 95% of intravenous inductions) has taught that induction is effervescent; hesitation in following through with maintenance agents often results in the patient awakening, sometimes producing hazardous patient management problems. It is obvious that midazolam is slower acting and that there may be more margin for hesitation, still I would not count on this as a dependable coverup for poor technique. My dosage recommendations are based upon deductions derived from the data and consideration of the fact that research conditions are often artificial.

In the Original NDA submission, the sponsor proposes the following dosage for induction of anesthesia: "In the absence of premedication, total induction dose can vary over a wide range (0.15-0.65 mg/kg), an average adult requiring 0.35 mg/kg for induction. When a sedative (particularly a narcotic) premedication is used, the average induction dose is lowered to approximately 0.2 mg/kg (range 0.15 to 0.35 mg/kg)."

I have gone over my review to select studies which seem to cast some light on dosage recommendations for induction of general anesthesia. The studies not on this list generally deal with unsatisfactory dosage recommendations, particularly inductions that were too slow or which had to be completed by other agents (not that the latter is always undesirable, because it may often be the simplest way to get the job done, but that it may not cast light on the induction dose of midazolam):

**Intravenous Induction Doses Without Premedication
or with Only Anticholinergic Premedication:**

#2213: The initial dose (and 25% increments at 2 minutes after initial dose) varied but mean dose of 0.37 mg/kg, major part administered over 5 seconds, was successful in a mean time of 121 seconds.

SPECIAL NOTE: This review is concerned with an unusually large number of studies. Please read the **CONCLUSIONS AND RECOMMENDATION** Sections, conveniently placed first, before checking the Index (placed after a review of the package insert) to determine what else to read. The **CONCLUSIONS** Section makes frequent reference to individual studies judged worthy of supporting Conclusions. Some studies are cited more than once.

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**Intravenous Induction Doses Without Premedication
or with Only Anticholinergic Premedication:**

#2213: The initial dose (and 25% increments at 2 minutes after initial dose) varied but mean dose of 0.37 mg/kg, major part administered over 5 seconds, was successful in a mean time of 121 seconds.

#2210: ASA Risk III patients (close enough to "debilitated" patients as discussed in the package insert) received initial dose of 200 ug/kg over 60 seconds, adjusted upward from 175 ug/kg in the early cases. The usual 25% of the induction dose was administered every 2 minutes if needed. Mean dose was 211 ug/kg and the mean induction time was 119 seconds.

#2212A: Crossover comparison of midazolam maleate and midazolam hydrochloride. The dose of 0.3 mg/kg (technically 0.31-0.32 mg/kg) sufficed in 93-104 seconds.

Studies #2089A, 2088A, 2087A, 2082A & 2090A, premedication studies, are discussed in the next section. Control patients (no premedication) required mean of 0.337 mg/kg (127 seconds).

**Intravenous Induction Doses With Central Nervous System Depressant
Premedication (other than anticholinergics alone):**

#2121: Fentanyl 2 ug/kg was administered intravenously 5 minutes before induction. Midazolam 0.2 mg/kg, administered over 30 seconds, produced general anesthesia in 106 seconds. Technically, some patients received 25% at 2 minutes so that the mean dose was 0.21 mg/kg.

#2066E: Premedication consisted of meperidine 1 mg/kg i.m. Midazolam 0.2 mg/kg was administered over 20 seconds, with the usual 25% increments at 2 minutes if needed. The mean total dose was 0.276 mg/kg and the mean time was 119 seconds.

Studies #2089A, 2090A, 2082A, 2087A and 2088A: Various investigators tested various oral and intramuscular premedication agents, administered one hour before anticipated intravenous induction with midazolam: Innovar 0.02 ml/kg i.m. (each ml contains 0.05 mg of the narcotic fentanyl and 2.5 mg of the butyrophenone droperidol), hydroxyzine 100 mg orally, secobarbital 200 mg orally, morphine 0.15 mg/kg i.m., and diazepam 10 mg orally. These may be considered together because the premedication selected seemed to make little difference when those patients who did not receive premedication were compared to those patients who received premedication; the possible exception is 10 mg of oral diazepam, because there was a suggestion that this premedication regimen (dose or timing) was less effective than the others.

The initial doses were in the 0.15-0.4 mg/kg range, adjusted upward by ongoing analysis of the data on the first cases. The initial dose was administered over 30 seconds, followed by 25% increments every 2 minutes.

Without premedication - The mean total dose in these patients who served as controls was 0.337 mg/kg and the induction time was a mean of 167 seconds.

With premedication - The mean dose in premedicated patients was 0.225 mg/kg and the mean induction time was 127 seconds.

The artificial slowness of induction in this study should not detract from the lesson that we can learn about the value of premedication, almost any reasonable premedication it seems.

#2192: Fentanyl 1.5 ug/kg was administered intravenously five minutes before induction with midazolam. The dose of 200 ug/kg midazolam, administered over 30 seconds, sufficed in all cases in about 60 seconds.

#2254: Meperidine 1 mg/kg i.m. was administered one hour before anticipated induction. The single dose of 300 ug/kg, administered over 20 seconds, was always effective in two minutes (not timed). This was primarily a pancuronium interaction study.

#2255: Meperidine was administered i.m. or i.v. in the dose of 1 mg/kg, one hour before anticipated induction. Midazolam 300 ug/kg, administered over 20 seconds, was always effective in 2 minutes (not timed). This was primarily a special study of succinylcholine interaction.

#2139B: ASA Risk III patients, mainly for peripheral vascular surgery (close enough to the "debilitated" patients referred to in the package insert). Morphine was administered i.m. one hour before anticipated induction and i.v. before placement of the central venous catheter while the patients were still awake, doses individualized. The dose of midazolam was 0.15 mg/kg, administered over 30 seconds. This produced a mean induction time of 94 seconds and a median induction time of 40 seconds, but the range was 20-510 seconds. This dose seems to have worked in most poor risk patients studied but we are certainly approaching the lower limits for consideration in any patients studied so far.

2139: ASA Risk I and II patients who because of the anticipated surgery required placement of a central venous catheter. Morphine i.m. and i.v. was administered as in #2139A, directly above, dose individualized.

The dose of 0.25 mg/kg midazolam was administered over 30 seconds. Nineteen of 21 patients were asleep in a mean time of 31 seconds (range 3-60 seconds). The other two were hard to get asleep for whatever reason.

#1011: Induction and maintenance study in patients premedicated with morphine 0.1 mg/kg i.m., 1-2 hours before induction. In the induction part of the study, the dose of 200 ug/kg, administered over 5-10 seconds, sufficed.

#2085A: Comparison with and without fentanyl. Without fentanyl, the mean dose of 0.234 mg/kg sufficed for induction in a mean of 83 seconds. With fentanyl 1.5 ug/kg i.v., 5 minutes before induction, the mean dose of 176 ug/kg sufficed in a mean time of 67 seconds.

#1092A: In patients undergoing myocardial revascularization, morphine was administered i.m. 60-90 minutes before induction; the dose of morphine was individualized.

Midazolam 0.2 mg/kg worked in a mean time of approximately 25 seconds.

Now, where did the upper limit of 0.65 mg/kg come from? M. Melvin of UCSF (protocol #2152A) did a special study of the effect of midazolam on minimum alveolar concentration of halothane (MAC). It was necessary to administer a dosage range, and the doses of 0.15, 0.3, 0.45 and 0.6 mg/kg midazolam were administered through a free running intravenous line at the approximate rate of 0.075 mg/kg/minute. The experiment did not require that induction be completed with midazolam, and indeed many of the inductions were completed with halothane. In the 37/51 cases completed with midazolam, the mean dose was 0.21 mg/kg but it does not appear that any patients received close to this dose (the closest actual doses being 0.15 and 0.3 mg/kg).

The dose of 0.6 mg/kg seems safe, based on these data, but it also appears to be a dose that would seldom be considered. If induction is incomplete with a large dose of midazolam, induction can be completed with a volatile liquid inhalational anesthetic, such as halothane, in most cases. I would only consider continuing with midazolam if there were some reason to avoid volatile liquid inhalational anesthetics and/or alternative agents. Still the dose of 0.6 mg/kg should not be prohibited as long as it is stated that some lower dose will suffice in most cases.

These data, plus some general dosage tables by age and ASA status in Volume 1.5 (pages 15-17), lead me to conclude the following about dosage:

1. In average adults under the age of 55 years, unpremedicated, the initial dose of 0.3-0.35 mg/kg midazolam administered over 20-30 seconds is recommended, allowing up to 2 minutes for effect. If needed to complete induction, increments of approximately 25% of the initial or recommended dose are suggested.
2. Unpremedicated patients over the age of 55 years usually require less midazolam for induction. An initial dose of 0.3 mg/kg is recommended.
3. Unpremedicated patients with severe systemic disease or other debilitation usually require less midazolam for induction. An initial dose of 0.2-0.25 mg/kg is recommended in such patients. In some cases, as little as 0.15 mg/kg may suffice.
4. Individual response is variable, particularly when a narcotic premedicant is not used. In resistant cases, up to 0.6 mg/kg total midazolam may be used for induction, keeping in mind that larger doses may prolong recovery. In most cases involving large doses and unsuccessful induction, induction may, instead, be completed with other inhalational or intravenous agents.
5. With successful premedication, particularly with narcotics, the range of recommended doses is 0.15 to 0.35 mg/kg:

In average adults below the age of 55 years, the dose of 0.25 mg/kg administered over 20-30 seconds will usually suffice, allowing up to 2 minutes for effect.

The initial dose of 0.2 mg/kg is recommended in patients over the age of 55 years.

Reduced doses are recommended in patients with severe systemic disease or other debilitation; in some cases, as little as 0.15 mg/kg may suffice.

If needed to complete induction, increments of approximately 25% of the initial or recommended dose are suggested.

II. Amnesia or Impairment of Recall?: The sponsor wants to use the term "---anterograde amnesic effect---." They have certainly studied the effect of midazolam on impairment of recall and, in the opinion of this reviewer, are entitled to claim that midazolam impairs recall. The following are considered by this reviewer to be acceptable studies of impairment of recall:

Fragen #2286, an intramuscular premedication study of the dose of 0.08 mg/kg; some patients also received atropine or scopolamine. I conclude from these data that this dose i.m. may produce impairment of recall for 30-60 minutes. About half of the patients could not recall the memory card shown to them 30 minutes after injection but few forgot the memory card shown to them 90 minutes after injection. Actual incidence of impairment of recall (reviewer's speculation) should be higher, since testing conditions involved reinforcement. Impairment of recall following intramuscular injection of 0.08 mg/kg should, never-the-less, not be oversold on the basis of this study.

Fragen #2085A, an intravenous induction study. Props were shown when patients became oriented after surgery, following induction of anesthesia with various doses of midazolam. Impairment of recall was noted to some extent in about 90% of the patients and seemed independent of fentanyl, the premedication administered to some of the patients; this impairment of recall was total (no props recalled with reinforced testing) in about 60% of the cases and again fentanyl seemed to make no difference. The comparative drug, thiopental, was associated with no impairment of recall in about 66% of the cases.

Fragen #2192, an intravenous induction study. This was a study of the effects of age on midazolam requirements in patients who received 1.5 ug/kg fentanyl and 200 ug/kg midazolam. Eleven of 12 older patients (aged 49.75-60 years) had total impairment of recall as did 8/12 in the younger (aged 18-30 years) group; 4/12 younger patients had partial impairment of recall and so did the remaining older patient. Testing was as for Fragen #2085A.

Way & White #2202, an intravenous induction study. When patients were judged fit for discharge from the recovery room, they were shown pictures of 10 common objects. At later reinforced testing, those patients who received 0.3 mg/kg midazolam for induction manifested total impairment of recall in 31% of the cases, partial in 31% of the cases and none (if 5-10 of the pictures were recalled) in 37.5% of the cases. Ketamine and

thiopental were not reasonably associated with impairment of recall under the conditions of this test; a lower dose of midazolam (0.15 mg/kg), combined with ketamine, was also associated with less impairment of recall than the 0.3 mg/kg dose.

Reitan & Porter #2121, an intravenous induction study. The mean induction dose of midazolam was 0.21 mg/kg and testing was as for Fragen #2085A. Twenty of 24 patients manifested complete impairment of recall (83.3%) and 4/24 manifested partial impairment of recall (16.6%). In the thiopental comparison group, complete impairment of recall was noted in 38.4% of cases (10/26) and partial impairment was noted in 11.5% of cases (3/26); this was higher than in other studies. Fentanyl was administered intravenously in the dose of 2 ug/kg about 5 minutes before induction.

The sponsor has proposed the following for the INDICATIONS section of the package insert: "When diminished recall of an uncomfortable, unpleasant or painful procedure or surgery is desired, midazolam intravenously or intramuscularly can be particularly useful because of its prominent anterograde amnesic effect. Where recorded, anterograde amnesia was reported in 90% of patients receiving midazolam intravenously for induction of anesthesia and in 73% of patients receiving midazolam intramuscularly for preoperative medication. Seventy-three percent of patients in the endoscopy studies had no recall of introduction of the scope."

The package insert will be reviewed later. Some variation of the statement about induction dosage should be allowed in an appropriate part of the package insert. The data in Fragen #2286 does not support such a strong statement about intramuscular premedication. Disposition of endoscopy statement is up to the Group Leader (H.D.), who reviewed these studies.

III. Recovery: Recovery from anesthesia is dependent on all anesthetic agents employed, however the tests of recovery when midazolam is employed for induction of general anesthesia are pretty consistent. Patients generally awaken a little slower than those who received thiopental for induction, but the difference between drugs is of borderline clinical significance or no clinical significance. Most gross tests of recovery are complete in 2 hours (orientation, judgement that the patient is fit for discharge from the recovery room, able to stand and walk, return of baseline Treiger competency) but thiopental patients again generally pass these tests faster than midazolam patients. Return of normal reaction time under stress during the operation of hazardous machinery, such as an automobile, has not been determined. At a minimum, nobody should operate an automobile or other hazardous machinery on the day of anesthesia and surgery which includes use of midazolam; the recovery data are encouraging but some extra margin must be allowed until more definitive tests are devised.

For study of recovery, I recommend the following studies:

2121 Porter & Reitan	2210 Grambling
2213 DuPen & McLaren	2212A Bivens & Mahaffey
2192 Fragen	1011 Reves
2085A Fragen	

Note also 2201A Fragen, a study of i.m. premedication going up to 0.075 mg/kg. In this volunteer study the Treiger test took 6 hours to return to baseline competency. These volunteers were generally more sedated than actual patients, but the dosage is also lower than for intravenous induction studies. This reinforces my impression that we don't have all of the answers about operating hazardous machinery, automobiles, etc.

IV. Dosage for Intramuscular Premedication: Here is what I learned about i.m. premedication. Keep in mind that claims about relief of situational anxiety are under review by the staff of HFN-120:

Fragen #2201A: Volunteer crossover study employing 0.05 and 0.075 mg/kg i.m. The dose of 50 ug/kg produced inadequate sedation and the dose of 75 ug/kg produced satisfactory sedation. A larger dose of 100 ug/kg was planned if the results of lower doses justified higher dosage; it was decided, after only one subject had received 100 ug/kg, that the 75 ug/kg dose was satisfactory and that no additional investigation of the 100 ug/kg dose was justified. In general, these volunteers were more sedated than surgical patients in other studies.

Fragen #2286: The dose of 0.08 mg/kg was administered i.m. Sedation was in the desired range at 30, 60 and 90 minutes. Peak was at 30-60 minutes, slightly less at 90 minutes.

Pooled Study #2199A, Miller, Slavic-Svircev, Vinik & Giesecke: The i.m. dose was 70 ug/kg. Onset was noted at 15 minute testing; sedation was in satisfactory range at 30 minute testing, peaking at 45 and 60 minutes (last time interval tested). The induction dose of thiopental was moderately less (3.6 mg/kg versus 4.2 mg/kg) after midazolam, premedication than after placebo.

Pooled Study #2198A, Artru, Dhamne, Seifen, Wright & Watson: The dose of 70 ug/kg i.m. produced sedation within the desired range in 30 minutes, peaking at 60 minutes (last time interval tested).

These data support the dosage recommendations proposed by the sponsor for the package insert: 0.07-0.08 mg/kg i.m. (approximately 5 mg i.m. for an average adult).

V. Respiratory:

Intramuscular: See T. C. Smith Study No. 2325A. The dose of 70 ug/kg i.m. did not significantly depress the respiratory response to carbon dioxide stimulation and did not add to the depression of respiratory response to carbon dioxide noted after the administration of i.m. morphine.

Intravenous: Underventilation and transient apnea are frequently noted after intravenous induction of anesthesia with midazolam. This is so routine for general anesthesia as to be of no special concern; management by most trained anesthetists is about as automatic as using the brakes on a car when indicated.

Study No. 2206A, Rehder: Pulmonary Mechanics. The initial intravenous dose of 0.09 mg/kg was found to be associated in volunteers with a sedated but awake state, maintained afterwards by intravenous infusion at a rate of 25 to 50 ug/minute. Sedation with midazolam intravenous did not affect the functional residual capacity or residual volume significantly. Pulmonary resistance and static recoil were also not affected by midazolam sedation. Total lung capacity and peak expiratory flow decreased significantly, perhaps because of sedation. Maximum expiratory flow at 50% of awake total lung capacity (V_{max}) was greater during the sedated state than the awake state. Static compliance increased during the sedated state. The sponsor concludes that midazolam does not increase the work of breathing and does not cause bronchoconstriction.

Study #2138, T.C. Smith: The intravenous dose of 200 ug/kg administered to volunteers significantly alters the ventilatory response to carbon dioxide for the fifteen minute test period. In contrast, the slope was 84% of control three minutes after the intravenous administration of thiopental 3.5 mg/kg. Ventilatory response to carbon dioxide was greatly altered during 20 minutes of testing in patients with chronic obstructive pulmonary disease (COPD).

VI. Circulatory:

Study 2139, Lebowitz: ASA I & II patients who required arterial and central venous catheters for relatively extensive surgery. The dose of 250 ug/kg i.v. midazolam was associated with decrease in mean arterial pressure, heart rate, cardiac output, stroke volume and systemic vascular resistance in patients who were also premedicated with i.m. and i.v. morphine. These data suggest a favorable oxygen demand-supply ratio, but these patients did not have symptomatic coronary artery disease. Mean right atrial pressure was elevated about 1 mmHg after administration of midazolam. Trends were the same following thiopental 4 mg/kg, except that heart rate fell more, cardiac output fell more and mean right atrial pressure rose about 2 mmHg.

Study #2139B, Lebowitz: ASA Risk III patients who required arterial and central venous catheters prior to surgery, mostly peripheral vascular surgery. Premedication was again with morphine i.m. and i.v. The induction dose of midazolam was 150 ug/kg. Mean arterial pressure, heart rate, stroke volume, systemic vascular resistance and cardiac output fell moderately, while mean right atrial pressure rose about 1.5 mmHg. Thiopental was associated with no change in stroke volume and little change in cardiac output (3 mg/kg); systemic vascular resistance fell more in the thiopental group and mean right atrial pressure changed about as much as for midazolam (lower baseline). This again suggests favorable oxygen demand-supply ratio.

No extreme changes were noted: For instance, in both 2139 and 2139B the baseline heart rate was approximately 85 per minute and the decrease was into the upper 70's per minute. I mention this because in Reves Protocols 1092A and 1092, discussed next, heart rates were very slow to begin with and then rose moderately; thus the direction of heart rate change was different for Lebowitz than for Reves.

Study #1092A, Reves. Patients were undergoing myocardial revascularization surgery for which invasive monitoring was set up in advance. Preparation for surgery seemed geared towards avoiding agents and incidents which might accelerate heart rate; the majority of patients were chronically on propranolol. The result was that baseline heart rate was less than 65 minute.

Patients were premedicated with i.m. morphine (and scopolamine). The administration of 0.2 mg/kg midazolam was associated with a moderate increase in heart rate to the 70-75/minute range. This was associated with a moderate drop in mean arterial pressure. Mean pulmonary artery pressure fell moderately, as did right atrial pressure. Rate-pressure product and left ventricular stroke work index fell, suggesting favorable ratio of oxygen demand to supply. Midazolam did not protect against the tendency of pancuronium to elevate heart rate.

Study No. 1092, Reves. This study turned out to be a preparation for Study #1092A, needed for organizational purposes. Patient population, premedication, etc. was as for 1092A. Heart rate was even slower to start with (mean 54.8/minute in the midazolam group). Results were about the same as for 1092A.

There were three cases described as "severe" (greater than 50% or required treatment) drops in blood pressure around the time of induction (Fragen 830A, one case and Reves 1092A, two cases). These cases were transient and did not require treatment. On the basis of the information offered in the case reports, there seem to be other factors involved which preclude incriminating midazolam.

I checked many of the cases described as "severe" (greater than 50% or required treatment) elevations in blood pressure and/or pulse. Many of these observations were associated with endotracheal intubation under light or very light general anesthesia. It seems unreasonable to incriminate midazolam. Treatment here is simpler, deepen anesthesia, so N_2O was often used. See, for instance, my summary of Study No. 2202 (Way & White).

The sponsor proposes the following for the package insert (Clinical Pharmacology Section): "In cardiac hemodynamic studies intravenous midazolam at doses of 0.15 to 0.2 mg/kg did not have deleterious effects on cardiac hemodynamics. Although midazolam may cause modest decreases in mean arterial pressure, baroreceptor response is not affected and decreases in arterial pressure are accompanied by increases in heart rate."

I would modify this: Baroreceptor response is, in the opinion of this reviewer, an indirect deduction that had best not be discussed in the package insert. On the other hand, some mention of favorable indirect estimate of oxygen demand supply ratio should be inserted. The increase in heart rate is seen only in some studies (mainly Reves 1092A and the less important Reves 1092) with very slow heart rates to begin with, the majority of patients being on propranolol. Decrease in heart rate is seen in other studies conducted in patients without symptomatic ischemic heart disease but with faster heart rates to start with. Definitive recommendations about the package insert will be written later.

N-18654-5

VII. Combined Induction and Maintenance:

The sponsor claims the following for the package insert: 1. INDICATIONS - "...and for maintenance of anesthesia as a component of a balanced anesthetic technique." 2. DOSAGE AND ADMINISTRATION - "Midazolam can also be used during the progress of anesthesia as a component of balanced anesthesia technique for maintenance by injection of increments of midazolam whenever anesthesia lightens. ... Incremental injections of approximately 25% of the induction dose should be given in response to lightening of anesthesia and repeated as necessary."

The following studies support such use:

Study No. 2152A, M. Melvin. This study shows that midazolam decreases the minimum alveolar concentration (MAC) of halothane in a dose related manner. This establishes that midazolam contributes to general anesthesia, less halothane being needed to inhibit patient response to painful stimuli. This is the most important study in support of use of midazolam for maintenance, making up for any shortcomings that the other studies may have.

Study No. 1011, J. G. Reves. Short surgical procedures in ASA Risk I & II patients, mean duration 59 minutes. The following contributed to anesthesia: morphine 0.1 mg/kg i.m, midazolam 200 ug/kg for induction and nitrous oxide in oxygen. Thirteen of 20 midazolam patients for analysis received midazolam during maintenance; increments were 1/3 of the induction dose, up to 3 such doses. The mean maintenance dose in these 13 patients was 130 ug/kg total (range 70-210 ug/kg). Two patients received non-protocol maintenance agents (droperidol, enflurane or halothane). Succinylcholine, a muscle relaxant of short duration, was also used and could have provided for lighter anesthesia but would not mask all signs used to decide when to administer increments of midazolam. On balance, this reviewer has the impression that midazolam made a contribution to maintenance.

Study No. 2085A, R. Fragen. This study would seem at first to cast little light on use of midazolam for maintenance, but we must remember that balanced anesthesia is the use of a combination of parenteral medications to supplement subpotent anesthetics (the only subpotent anesthetic which really counts today is nitrous oxide, ethylene having been discarded and relegated to the ripening of bananas long ago because of its explosive properties and unpopular odor). We must consider midazolam use here in conjunction with intravenous fentanyl, the other parenteral drug used to supplement nitrous oxide. Some patients received fentanyl 1.5 ug/kg intravenously 5 minutes before induction, and the control group did not. Duration of anesthesia was approximately 17 minutes for each group. In those patients who did not receive fentanyl, the mean induction dose was 260 ug/kg midazolam. In those patients who received fentanyl, the mean induction dose was 180 ug/kg and the time of induction was shorter (mean 67 seconds versus mean 83 seconds).

Increments for maintenance were required in 8/26 patients in the group which did not receive fentanyl. In the group which did receive fentanyl, 5/25 received maintenance midazolam. The dose per minute of midazolam, for maintenance, was lower in those patients who received fentanyl (0.005 mg/kg/minute versus 0.009 mg/kg/minute). This study would hardly stand by itself to support use of midazolam for maintenance but when considered in the light of the other two studies, especially the MAC study, it adds support. This study was valuable for other reasons (study of recovery and impairment of recall).

I would add only one qualification to the sponsor's claim. Midazolam is effective for maintenance of anesthesia as a component of balanced anesthesia but only short surgical procedures have been studied, therefore it should only be recommended for maintenance during short surgical procedures.

VIII. Intraocular Pressure:

The sponsor proposes the following in the DOSAGE AND ADMINISTRATION section of the package insert contained in the original NDA submission: "It (midazolam) can also be used in patients with open angle glaucoma."

In CONTRAINDICATIONS, the following appears: "It (midazolam) is also contraindicated in patients with acute narrow angle glaucoma. However, midazolam does not cause an increase in intraocular pressure and may be used in patients with open angle glaucoma."

The reference cited is Fragen Study No. 2027A. That was a study of intraocular pressure following induction with midazolam in ASA Risk I & II patients without increased intraocular pressure. Intraocular pressure fell after midazolam administration, and after administration of comparative induction agents. None of the drugs tested, including midazolam, protected against the rise in intraocular pressure associated with succinylcholine administration or endotracheal intubation.

The Contraindication appears generic for benzodiazepines. In the absence of studies in patients with open angle glaucoma, the generic statement that benzodiazepines should not be used in such patients unless they are receiving appropriate therapy should apply.

IX. Cerebrospinal Fluid Pressure:

The sponsor proposes the following for the initial DOSAGE AND ADMINISTRATION section of the package insert: "Midazolam can be used in neurosurgical patients with increased intracranial pressure."

This is based upon Cottrell, 2188A, a study incomplete at the time of NDA submission. From the early data of that study we see that midazolam lowers intracranial pressure slightly in patients with normal intracranial pressure but decreased compliance (neurosurgical patients with a subarachnoid screw in place prior to induction). At endotracheal intubation, intracranial pressure again rose, but only to baseline measurement and only transiently.

In Ballinger, 1033, we see that midazolam administration was associated with a moderate decrease in cerebrospinal fluid pressure in ASA Risk I & II patients with normal cerebrospinal fluid pressure scheduled for abdominal or lower extremity surgery under spinal anesthesia.

I suggest a discussion which sticks to the conditions of these two experiments, preferably in the CLINICAL PHARMACOLOGY or PRECAUTIONS section.

X. Neuromuscular Blockage Interaction:

The sponsor proposes the following for the PRECAUTIONS section of the package insert, under Drug Interactions: "Midazolam has been shown to potentiate the effect of pancuronium. A clinically nonsignificant prolongation of neuromuscular blockade is seen when midazolam is administered concomitantly with succinylcholine."

I would recommend simply saying that use of midazolam for induction of general anesthesia does not cause a clinically significant change in the onset and duration of a single intubating dose of succinylcholine and that preliminary data reveals no clinically significant drug interaction with pancuronium. See Cronnelly, #2255 and 2254.

XI. Ketamine Interaction:

The sponsor proposes the following for the PRECAUTIONS section of the package insert (Drug Interactions): "Intravenous midazolam inhibits the cardiostimulatory response and unpleasant emergence sequelae frequently resulting from ketamine administration."

The reference is Way & White, Study No. 2202. This would certainly seem true for emergence sequelae based upon the results of that study, but there are two things to keep in mind: 1. This is based upon limited clinical experience of 18 patients receiving ketamine for induction and 18 patients receiving a combination of ketamine and midazolam for induction, 2. Those patients who received both ketamine and midazolam received only half of the dose of ketamine when it was used alone (in fairness it should also be noted that the same is true for midazolam).

I suggest deleting this statement from the original package insert, based upon insufficient data.

XII. Diazepam Shortcomings as a Parenteral Medication:

Clinicians who use parenteral diazepam frequently complain that the pharmaceutical preparation is water insoluble and that it is irritating on intravenous and intramuscular injection. Bioavailability following intramuscular injection is regarded by some clinicians as unpredictable. In addition, diazepam is a longer acting drug than midazolam. This review is not intended to prove these shortcomings; any confirmation, if needed, will have to come from HFN-120.

Irritation on injection does not seem to be a big problem with midazolam aqueous solution. Bioavailability following intramuscular injection has been established. These advantages, in the light of established efficacy and the lack of safety problems when used properly in clinical anesthesia, suggest that there is a place for parenteral midazolam in the practice of medicine.

XIII. Compatibility:

In these studies, midazolam solution has been used along with most standard drugs, or representatives from each group of drugs, used in anesthetic practice. These were not subtle studies of minute drug interaction but no clinical incompatibilities were revealed. It seems reasonably established that midazolam solution fits in with more established drugs for use in anesthetic practice.

XIV. Serious Complications:

The following serious complications have been reviewed:

Protocol 2188A, J. Cottrell: Two deaths in patients with intracranial lesions: One due to intracranial bleeding and one due to pulmonary embolism. The investigator's indifferent handling of these adverse experiences is discussed in the review. There is no reasonable association between the administration of midazolam and these two fatal adverse experiences.

Protocol 2210, Z. Gramling: One patient who received diazepam as a test drug died 11 days after test drug administration of generalized carcinomatosis. There is no reasonable association between the fatal outcome of this case and test drug administration.

Protocol 2210A, R. Wright: A myocardial infarction developed during or after anesthesia and surgery. About 75 seconds after midazolam administration for induction of anesthesia, the blood pressure fell to 101/58, with a heart rate of 94 per minute. This was treated with phenylephrine; the phenylephrine, in turn, had to be treated with halothane to manage the hypertension which resulted. The infarction seems related to many events around the time of induction; on the basis of this information, phenylephrine may have turned out to be more of a liability than an asset. I judge that midazolam was not the deciding factor in this adverse experience but that it must be considered part of the overall picture. The investigator was not prompt and thorough in reporting this adverse experience and, thus, it is doubtful that we will ever know more. The patient, a female of about 64 years, recovered from surgery and the myocardial infarction. She had no additional coronary artery problems of a symptomatic nature at the last known followup.

Protocol 2088A, R. Hicks: This patient received the control drug, thiopental. She was a 29 year old female scheduled for biopsy of a neck mass. She unexpectedly developed hypotension and ECG changes after induction of anesthesia. The temporal events and ECG changes led to a diagnosis of subendocardial myocardial infarction. Recovery was uneventful, for a myocardial infarction, and the patient was discharged for later followup without need for medication in the meanwhile. Thiopental did contribute to the unexpected alteration in perfusion, but can hardly be incriminated alone.

Protocol 2234A, P. Kvale: This is based on information which came in after submission of the NDA. Dr. Kvale studied intravenous midazolam to facilitate bronchoscopies (with proper topical anesthesia). Two patients who received midazolam (one 65 year old female and one 48 year old male) died within a few days of test drug administration of disseminated carcinoma, one seven days later and one four days later. Neither adverse experience appears reasonably associated with test drug administration. See SERIOUS ADVERSE EXPERIENCE UPDATE portion of this review.

In addition, on 20 June 1984 I was notified that a 21 year old male medical student participated in a pharmacokinetic study of i.m., i.v., oral and "PR" midazolam in Cardiff, England (October 1983). In January 1984 the subject developed thrombocytopenia, progressing first to pancytopenia and later aplastic anemia. The patient is currently in critical condition and not expected to live. There are currently insufficient data to permit evaluation and, therefore, evaluation is deferred. In the meanwhile, no recommendations will be made on the basis of this case. See SERIOUS ADVERSE EXPERIENCE UPDATE portion of this review.

RECOMMENDATION:

This application is approvable under Section 505 (b) (1) of the Federal Food, Drug, and Cosmetic Act.

With prescribing information changes, this application is approvable under Section 505 (b) (6).

David Lawrence Scally

David Lawrence Scally, M.D.
Medical Officer HFN-160

REVIEW OF THE PACKAGE INSERT:

The next section contains my version of a complete package insert, derived from a recent draft by ROCHE. Note that several pieces of information will have to be filled in by ROCHE. The sponsor should be allowed to discuss this revision of the package insert as soon as possible.

NDA 18-654

HFN-160

HFN-120

HFN-340

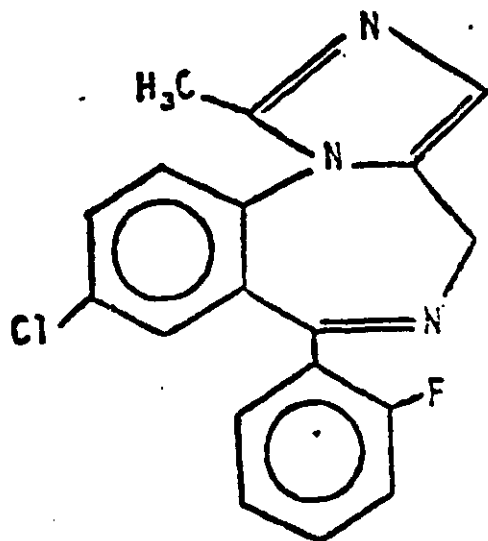
R/D DLScally 6/27/84

R/D Init. by HLDickstein 7/26/84, PGWalters for PHRussell 7/30/84

FT OLA W1630N A0088N 8/1/84

DESCRIPTION: VERSED (midazolam HCl/Roche) is a benzodiazepine with sedative, hypnotic, amnestic and anxiolytic properties. Injectable VERSED is a sterile parenteral dosage form for intravenous or intramuscular injection. Each ml contains midazolam hydrochloride equivalent to 5 mg midazolam compounded with 0.8% sodium chloride and 0.01% disodium edetate, with 1% benzyl alcohol as preservative; the pH is adjusted to approximately 3 with hydrochloric acid and, if necessary, sodium hydroxide.

Chemically, midazolam is 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine. It is a white to light yellow crystalline compound, insoluble in water; the hydrochloride salt is soluble in aqueous solutions. Midazolam has a calculated molecular weight of 325.78 and the following structural formula:



CLINICAL PHARMACOLOGY: Midazolam is a short-acting central nervous system depressant which induces sedation, hypnosis and diminished recall.

The mechanism of action of the benzodiazepines is under continuous investigation. Benzodiazepines appear to intensify the physiological inhibitory mechanisms mediated by gamma-aminobutyric acid (GABA), the most common inhibitory neurotransmitter in the brain. In animal and human experiments, it has been shown that certain benzodiazepines combine in a selective, stereospecific fashion to receptor sites in the brain. These receptor sites are predominately located in neuronal surface membranes. The distribution of the binding sites within the CNS is widespread, occurring in major brain regions in varying concentrations.

Following intramuscular administration, onset of action of injectable VERSED is approximately 15 minutes with peak effect occurring 30 to 60 minutes following injection. When used intravenously as a sedative for endoscopic or other short therapeutic or diagnostic procedures, the end point of slurred

speech can be attained within 2.8 to 4.8 minutes, depending on the total dose administered and whether or not preceded by narcotic premedication. Induction of anesthesia for surgical procedures occurs in approximately 1.5 minutes when a narcotic premedicant has been administered and in 2 to 2.5 minutes without premedication or with a sedative premedication.

Midazolam, used as directed, does not delay awakening from general anesthesia. Gross tests of recovery after awakening (orientation, able to stand and walk, able to discharge from recovery room, return to baseline Treiger competency) are usually complete within 2 hours but may take up to 6 hours in some cases. When compared to patients who received thiopental, patients receiving midazolam generally recover at a slightly slower rate. Reaction time under stress (operating automobiles or other hazardous machinery) has not been studied.

About half of the patients who received 0.08 mg/kg of intramuscular midazolam manifested impaired recall of reinforced props for 30-60 minutes afterwards. Following intravenous induction of anesthesia with midazolam and later awakening in the recovery room, some impairment of recall is noted in over 90% of the cases; the majority of patients could identify none of the props shown at this time, despite reinforcement designed to assist recall.

The intravenous administration of midazolam decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This observation correlates with the dose of midazolam administered.

Intramuscular premedicating doses of midazolam do not depress the ventilatory response to carbon dioxide stimulation to a clinically significant extent. Induction doses greatly depress the ventilatory response to carbon dioxide stimulation for more than 15 minutes or longer than thiopental. Impairment of ventilatory response to carbon dioxide is more marked in patients with chronic obstructive pulmonary disease (COPD). Sedation with intravenous midazolam does not adversely affect the mechanics of respiration (resistance, static recoil, most lung volume measurements); total lung capacity and peak expiratory flow decrease significantly but static compliance and maximum expiratory flow at 50% of awake total lung capacity (V_{max}) increase.

In cardiac hemodynamic studies, induction with midazolam was associated with a slight to moderate decrease in mean arterial pressure, cardiac output, stroke volume and systemic vascular resistance. Slow heart rates (less than 65/minute), particularly in patients taking propranolol for angina, tended to rise slightly; faster heart rates (e.g., 85/minute) tended to slow slightly. Indirect estimates of myocardial oxygen demand versus supply (e.g., rate-pressure product, left ventricular stroke work index) suggest a favorable ratio.

Midazolam does not protect against the circulatory effects of succinylcholine administration or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

In patients without intracranial lesions, induction with midazolam is associated with a moderate decrease in cerebrospinal fluid pressure (lumbar puncture measurements), similar to that seen following use of thiopental. Preliminary data in intracranial surgery patients with normal intracranial pressure but decreased compliance (subarachnoid screw measurements) show a moderate lowering of intracranial pressure following induction with midazolam. Midazolam does not protect against the increase in intracranial pressure noted following administration of succinylcholine and/or endotracheal intubation during light general anesthesia.

Intraocular pressure measurements in patients without eye disease show a moderate lowering following induction with midazolam; patients with glaucoma have not been studied. Midazolam did not protect against the rise in intraocular pressure seen following administration of succinylcholine and/or endotracheal intubation.

The pharmacokinetic profile of midazolam in man is linear over the 0.05 to 0.6 mg/kg dose range. In normal subjects and healthy patients intravenous midazolam exhibited an elimination half-life of 2.5-2.8 hours (range: to be supplied), a large volume of distribution (0.8 to 1.86 L/kg) and a rapid plasma clearance (0.24 to 0.73 L/hr/kg).

Following intravenous administration, less than 0.03% of the dose is excreted in the urine as intact midazolam. Midazolam is rapidly metabolized to 1-hydroxymethyl midazolam which is conjugated with subsequent excretion in the urine. Approximately 45% to 81% of the dose is excreted in the urine as the conjugate of 1-hydroxymethyl midazolam, the major metabolite of midazolam. The half-life of elimination of 1-hydroxymethyl midazolam is similar to the parent compound. The concentration of midazolam is 10- to 30-fold greater than that of 1-hydroxymethyl midazolam.

In patients with congestive heart failure, there is a 2- to 3-fold increase in the elimination half-life and volume of distribution of midazolam; however, the total body clearance of midazolam remains unchanged at a single 5 mg intravenous dose of midazolam. There is no apparent change in the pharmacokinetic profile of midazolam following the intravenous administration of 5 mg of midazolam to patients with hepatic dysfunction. There is a 1.5- to 2-fold increase in elimination half-life, total body clearance and volume of distribution in patients with chronic renal failure.

The mean absolute bioavailability of midazolam following intramuscular administration is greater than 90%. The mean time of maximum midazolam plasma concentrations following intramuscular administration occurs within one-half hour postadministration. The elimination pharmacokinetic profile of intramuscularly administered midazolam is comparable to that observed following intravenous administration of the drug.

Midazolam is approximately 97% plasma protein-bound in normal subjects and patients with renal failure. In animals, midazolam has been shown to cross the blood brain barrier. In animals and in humans, midazolam has been shown to cross the placenta and enter into fetal circulation. It is not known whether midazolam is excreted in human milk.

INDICATIONS: Injectable VERSED is indicated --

intramuscularly as a preoperative medication for sedative (sleepiness or drowsiness) effects, diminished recall of perioperative events and for alleviation of the situational anxiety which may be present before the anticipated surgery;

intravenously as an agent for conscious sedation prior to short surgical, diagnostic, therapeutic or endoscopic procedures, such as bronchoscopy, gastroscopy, cystoscopy, coronary angiography and cardiac catheterization, either alone or in conjunction with a narcotic;

intravenously for induction of general anesthesia, preliminary to administration of other anesthetic agents. With the use of a narcotic premedicant, induction of anesthesia can be attained within a relatively narrow dose range and in a short period of time. Intravenous VERSED can also be used as a component of intravenous supplementation of nitrous oxide and oxygen (balanced anesthesia) for short surgical procedures; longer procedures have not been studied. When used intravenously, VERSED is associated with a high incidence of partial or complete impairment of recall for the next several hours, as determined by use of reinforced props (see Clinical Pharmacology).

CONTRAINDICATIONS: Injectable VERSED is contraindicated in patients with a known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma. Benzodiazepines may be used in patients with open angle glaucoma only if they are receiving appropriate therapy (see also Clinical Pharmacology).

WARNINGS: PRIOR TO THE INTRAVENOUS ADMINISTRATION OF MIDAZOLAM IN ANY DOSE, THE IMMEDIATE AVAILABILITY OF OXYGEN AND RESUSCITATIVE EQUIPMENT FOR THE MAINTENANCE OF A PATIENT AIRWAY AND SUPPORT OF VENTILATION SHOULD BE INSURED. Since intravenous midazolam depresses respiration (see CLINICAL PHARMACOLOGY), and since the combined effect of other drugs used for endoscopy or induction of general anesthesia cannot be predicted, it is recommended that intravenous midazolam be administered only during attendance by a person trained in the administration of general anesthesia and the maintenance of a patent airway.

Injectable VERSED should not be administered to patients in shock or coma, or in acute alcohol intoxication with depression of vital signs.

The hazards of intra-arterial injection of midazolam solutions in humans are unknown, therefore, extreme precautions against unintended intra-arterial injection should be taken. The following have been observed following injection in the _____ artery of _____ species): _____.

[to be supplied by sponsor, if available.] Extravasation should also be avoided.

When administering intravenous midazolam to special patient groups, it should be remembered that: Higher risk surgical patients and/or debilitated patients require less midazolam for induction of anesthesia, whether premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of midazolam. Patients with chronic renal failure have a 1.5-2 fold increase in elimination half-life, total body clearance and volume of distribution of midazolam. Patients with congestive heart failure have a 2-3 fold increase in the elimination half-life and volume of distribution of midazolam. Patients over the age of 55 years require less midazolam for induction of anesthesia, whether premedicated or not. Since elderly patients frequently have inefficient function of one or more organ systems, and since dosage has been shown to decrease with age, reduced initial dosage of midazolam is recommended and the possibility of profound and/or prolonged effect should be considered.

Concomitant use of barbiturates, alcohol or other central nervous system depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. When premedication with a narcotic is selected, it should be remembered that narcotics also depress the ventilatory response to carbon dioxide stimulation.

The decision as to when patients who received injectable VERSED, particularly on an outpatient basis, may again engage in occupations requiring complete mental alertness, operate hazardous machinery or drive a motor vehicle must be individualized. Gross tests of recovery from the effects of midazolam (see CLINICAL PHARMACOLOGY) cannot be relied on alone to predict reaction time under stress. This drug is never used alone during anesthesia and the contribution of other perioperative drugs and events can vary. It is recommended that no patient operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia and surgery, whichever is longer.

PRECAUTIONS: General: Since an increase in cough reflex and laryngospasm may occur with perioral endoscopic procedures, the use of a topical anesthetic agent and the availability of necessary counter measures are recommended. The use of a narcotic premedicant is recommended for bronchoscopies.

Intravenous doses of VERSED should be decreased by 25% to 30% for elderly and debilitated patients (See WARNINGS to DOSAGE AND ADMINISTRATION). These patients will also probably take longer to recover completely after VERSED administration for the induction of anesthesia.

Information for patients: To assure safe and effective use of benzodiazepines, the following information and instructions should be given to the patient when appropriate:

1. Inform your physician about any alcohol consumption and medicine you are now taking, including drugs you buy without a prescription. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol during benzodiazepine treatment.

2. Inform your physician if you are pregnant or are planning to become pregnant.
3. Inform your physician if you are nursing.

Drug interactions: The hypnotic effect of intravenous VERSED is accentuated by premedication, particularly narcotics (e.g., morphine and meperidine) and also secobarbital, Innovar (fentanyl and droperidol) and fentanyl. Consequently, the dosage of VERSED should be adjusted according to the type and amount of premedication administered. (See DOSAGE AND ADMINISTRATION.)

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following recommended use of intramuscular VERSED for premedication.

The additive effect of VERSED may result in a reduction of the inhalation anesthetic requirement during maintenance of anesthesia (see CLINICAL PHARMACOLOGY).

Data regarding subtle interaction between pancuronium and midazolam are inconclusive at the present time, however, midazolam and pancuronium have been used together in patients without clinically significant changes in dosage, onset or duration. Midazolam does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine. Midazolam does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium and does not protect against the blood pressure rise and/or pulse rate increase sometimes seen during endotracheal intubation under light or very light general anesthesia.

No significant adverse interactions with commonly used premedicants or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with results obtained in clinical laboratory tests.

Carcinogenesis, mutagenesis, impairment of fertility:

Carcinogenesis: Midazolam maleate administered as a dietary admixture for two years at the dosage of 80 mg/kg (228 times a human dose of 0.35 mg/kg) produced a marked increase in hepatic tumors in female mice.

The increased incidence of hepatic tumors in mice after prolonged dosing is considered to be secondary to the liver enlargement and hepatocellular hypertrophy due to microsomal enzyme induction. This finding is similar to that produced by phenobarbital and a variety of other hepatic microsomal enzyme inducers in mouse strains with a genetic predisposition to spontaneous liver tumors. Other than liver, no gross lesions suggestive of treatment-related neoplasia have been observed in the mouse study.

In a two-year dietary admixture study, a slight increase in the incidence of thyroid tumors was observed in male rats administered dosages of 80 mg/kg/day of midazolam maleate. The observed increase was limited to benign tumors; there was no increase in follicular carcinoma. The small magnitude of increase in the incidence of thyroid tumors is considered to be a marginal effect but related to treatment with high microsomal enzyme-inducing doses of midazolam. Microsomal enzyme inducers, such as phenobarbital, are known to be goitrogenic at high dosages in rodents resulting in increased thyroid weights, increased metabolism and turnover of thyroxine, and increased serum concentrations of thyroid stimulating hormone (TSH). A variety of goitrogenic substances are known to increase thyroid tumor formation in rodents as a result of a sustained increase in the level of TSH released from the pituitary. In humans, no evidence of hepatic enzyme induction with midazolam maleate has been found.

Mutagenesis: Midazolam maleate has been extensively studied in a variety of short-term tests to assess its genotoxic potential. The studies included Ames tests (with and without metabolic activation) using five different tester strains of *Salmonella typhimurium* and *E. coli* WP2 uvrA, a fluctuation test (without metabolic activation), tests with Chinese hamster lung cells and the diploid yeast strain *Saccharomyces cerevisiae* D7 (with and without metabolic activation), a mouse micronucleus test and chromosomal analyses using human lymphocytes. The results of all tests were negative.

Impairment of fertility: Studies in rats demonstrated that an oral dose of 16 mg/kg/day of an injectable formulation of midazolam maleate is essentially equivalent to an intravenous dose of 4 mg/kg/day of the injectable formulation. In a Segment I study of fertility and general reproductive performance in rats, dose-related sedative effects were noted in midazolam-treated male and female rats, but there were no adverse effects on parameters of fertility and general reproductive performance. The highest dose studied (16 mg/kg/day) was, on an equivalent intravenous basis, approximately 11 times a human dose of 0.35 mg/kg.

Pregnancy: Teratogenic effects: Pregnancy Category B.

Segment II teratology studies have been performed with midazolam maleate injectable in rabbits and rats at intravenous doses up to 2 and 4 mg/kg/day (approximately 5.7 and 11 times a human dose of 0.35 mg/kg), respectively, and have revealed no evidence of embryotoxicity or teratogenicity. In the rat teratology study, a slight increase in postimplantation loss, considered to represent cannibalism of pups prior to inspection of the litter, was noted in the litters of dams allowed to deliver at doses of 1 and 4 mg/kg/day.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic effects: In oral Segment I (fertility and general reproductive performance) and intravenous Segment III (perinatal and postnatal) studies with midazolam maleate injectable in rats, no adverse effects were noted on various reproductive parameters during gestation and lactation, including neonatal viability and growth of the pups, at doses of 0.2 to 16 mg/kg/day.

Labor and delivery: In humans, measurable levels of midazolam were found in maternal venous serum, umbilical venous and arterial serum and amniotic fluid, indicating placental transfer of the drug. Following intramuscular administration of 0.05 mg/kg of midazolam, both the venous and the umbilical arterial serum concentrations were lower than maternal concentrations. The degree of transfer of midazolam to the placenta has been found to be clearly lower than that of diazepam and transfer appears to take place more slowly than for oxazepam or lorazepam.

The use of injectable VERSED in obstetrics has not been evaluated in clinical studies; therefore, the drug is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness of VERSED in children below the age of 18 have not been established.

ADVERSE REACTIONS: Fluctuations in vital signs were the most frequently seen findings following parenteral administration of VERSED and included decreased tidal volume and/or respiratory rate decrease (25.2% following i.v. and 11.0% following i.m. administration) and apnea (16.8% following i.v. administration), as well as variations in blood pressure and pulse rate. These are common occurrences during anesthesia and surgery and are affected by the lightening or deepening of anesthesia, instrumentation, intubation and use of concomitant drugs. It should especially be noted that midazolam does not modify the circulatory effects of neuromuscular blocking agents or the tachycardia and blood pressure rises seen during endotracheal intubation under light general anesthesia. Three cases (___%) of transient blood pressure fall greater than 50% were repeated around the time of induction during clinical investigation.

Following intramuscular injection, local adverse effects at the injection site were reported as follows:

pain (3.7%)	induration (0.5%)
erythema (0.5%)	muscle stiffness (0.3%)

Headache was reported with an incidence of 1.3%.

The following adverse reactions were reported subsequent to intravenous administration:

hiccoughs (4.2%)	local effects at the i.v. site -
nausea (2.7%)	tenderness (5.9%)
vomiting (2.5%)	pain during injection (5.4%)
coughing (1.4%)	redness (2.8%)
"oversedation" (1.4%)	induration (1.8%)
headache (1.3%)	phlebitis (0.4%)
drowsiness (1.0%)	

Other adverse experiences, observed mainly following i.v. injection and occurring at an incidence of less than 1.0% are as follows:

Respiratory: Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea.

Cardiovascular: Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm.

Gastrointestinal: Acid taste, excessive salivation, retching.

CNS/Neuromuscular: Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, agitation, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence, dreaming during emergence, sleep disturbance, insomnia, nightmares, tonic/clonic movements, muscle tremor, involuntary movements, athetoid movements, dizziness, dysphoria, slurred speech.

Ophthalmic: Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids.

Integumentary: Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, erythema.

Miscellaneous: Yawning, lethargy, chills, weakness, toothache, hematoma.

DRUG ABUSE AND DEPENDENCE: Midazolam is subject to Schedule I.V. control under the Federal Controlled Substances Act of 1970.

Although there are inadequate data to determine the drug abuse and dependence potential of midazolam, the potential may exist for withdrawal symptoms following chronic oral administration, similar in character to those reported following abrupt discontinuance of oral benzodiazepines.

OVERDOSAGE: There have been no reports of injectable VERSED overdose. However, it can reasonably be assumed that the manifestations of midazolam overdose would be similar to those observed with other benzodiazepines, including sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma and untoward effects on vital signs. No evidence of specific organ toxicity due to midazolam overdose would be expected.

Treatment of overdose: Treatment of injectable VERSED overdose is the same as that followed for overdose with other benzodiazepines. Respiration, pulse rate and blood pressure should be monitored and general supportive measures should be employed. Attention should be given to the maintenance of a patent airway and support of ventilation. An intravenous infusion should be started. Should hypotension develop, treatment may include intravenous fluid therapy, repositioning, judicious use of vasopressors appropriate to the clinical situation, if indicated, and other appropriate countermeasures. There is no information as to whether peritoneal dialysis, forced diuresis or hemodialysis are of any value in the treatment of midazolam overdose.

DOSAGE AND ADMINISTRATION: Dosage should be individualized for maximum beneficial effect. Lower doses are required in elderly or debilitated patients. The dosage of intravenous VERSED administered should be adjusted according to the type and amount of premedication used. When intravenous use is indicated, oxygen, resuscitative equipment and personnel resources for the maintenance of a patent airway should be immediately available. (See WARNINGS section.)

Injectable VERSED may be mixed in the same syringe with frequently used premedicants: morphine sulfate, meperidine, atropine sulfate or scopolamine. Injectable VERSED is compatible with 5% dextrose in water, normal saline, and lactated Ringer's solution.

For intramuscular use, VERSED should be injected deep in a large muscle mass. Intravenous VERSED for endoscopy should be administered slowly; rapid injection may cause respiratory depression or apnea requiring assisted or controlled ventilation. For induction of general anesthesia, the initial dose should be administered over 20-30 seconds for optimum effect. Extreme care should be taken to avoid intra-arterial injection or extravasation (see WARNINGS).

INTRAMUSCULARLY

For sedation (sleepiness or drowsiness), diminished recall of peri-operative events and alleviation of situational anxiety which may be present before surgery.

USUAL ADULT DOSE

For premedication the recommended dose of VERSED is 0.07 to 0.08 mg/kg i.m. (approximately 5 mg i.m. for an average adult) approximately one hour before surgery. Onset is within 15 minutes, peaking at 30-60 minutes. It can be administered concomitantly with atropine sulfate or scopolamine hydrochloride and reduced doses of narcotics.

INTRAVENOUSLY

Endoscopic or Cardiovascular Procedures

For conscious sedation, VERSED can be used either alone or together with a narcotic immediately before the procedure with supplemental doses to maintain the desired level of sedation throughout the procedure. For perioral procedures, the use of an appropriate topical anesthetic is recommended. For bronchoscopic procedures, the use of a narcotic premedicant is recommended.

Titrate dosage to desired sedative end point, i.e., slurring of speech, with slow administration immediately prior to the procedure. Generally 0.1 to 0.15 mg/kg is adequate, but up to 0.2 mg/kg may be given, particularly when concomitant narcotics are omitted. Additional maintenance doses may be given in increments of 25% of the initial dose to maintain the desired level of sedation.

Narcotic premedication results in less variability in patient response. Dosage should be lowered by about 25% to 30% if a narcotic premedicant is used. Patients 60 years or older may require lower doses (by about 30%) than younger patients.

Induction of Anesthesia

For induction of general anesthesia, preliminary to administration of other anesthetic agents.

In the absence of premedication, an average adult under the age of 55 years will usually require an initial dose of 0.3-0.35 mg/kg for induction, administered over 20-30 seconds and allowing 2 minutes for effect. If needed to complete induction, increments of approximately 25% of the initial or recommended dose may be used; induction may instead be completed with volatile liquid inhalational anesthetics. In resistant cases, up to 0.6 mg/kg total midazolam may be used for induction, keeping in mind that larger doses may prolong recovery.

Unpremedicated patients over the age of 55 years usually require less midazolam for induction; an initial dose of 0.3 mg/kg is recommended. Unpremedicated patients with severe systemic disease or other debilitation usually require less midazolam for induction. An initial dose of 0.2-0.25 mg/kg will usually suffice; in some cases, as little as 0.15 mg/kg may suffice.

When the patient has received satisfactory sedative or narcotic premedication, particularly narcotic premedication, the range of recommended doses is 0.15-0.35 mg/kg:

In average adults below the age of 55 years, the dose of 0.25 mg/kg, administered over 20-30 seconds and allowing 2 minutes for effect, will usually suffice.

The initial dose of 0.2 mg/kg is recommended for good risk (ASA I & II) surgical patients over the age of 55 years.

In some patients with severe systemic disease or other debilitation, as little as 0.15 mg/kg may suffice.

Narcotic premedication frequently used during clinical trials included

fentanyl (1.5-2 ug/kg i.v., administered five minutes before induction), morphine (dosage individualized, up to 0.15 mg/kg i.m.), meperidine (dosage individualized, up to 1 mg/kg i.m.) and Innovar (0.02 mg/kg i.m.). Sedative premedicants were hydroxyzine pamoate (100 mg orally) and sodium secobarbital (200 mg orally). Except for intravenous fentanyl, administered five minutes before induction, all other premedications should be administered approximately one hour prior to the time anticipated for VERSED induction.

Injectable VERSED can also be used during maintenance of anesthesia, for short surgical procedures, as a component of balanced anesthesia. Effective narcotic premedication is especially recommended in such cases. Long surgical procedures have not been studied.

Incremental injections of approximately 25% of the induction dose should be given in response to signs of lightening of anesthesia and repeated as necessary.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED: All package configurations contain midazolam hydrochloride equivalent to 5 mg midazolam/ml.

1 ml ampuls--boxes of 10 (NDC 0004-xxxx-xx);
 2 ml ampuls--boxes of 10 (NDC 0004-xxxx-xx);
 1 ml vials--boxes of 10 (NDC 0004-xxxx-xx);
 2 ml vials--boxes of 10 (NDC 0004-xxxx-xx);
 5 ml vials--boxes of 1 (NDC 0004-xxxx-xx) and 10 (NDC 0004-xxxx-xx);
 10 ml vials--boxes of 1 (NDC 0004-xxxx-xx) and 10 (NDC 0004-xxxx-xx);
 1 ml Tel-E-Ject^(R) disposable syringes--boxes of 10 (NDC 0004-xxxx-xx);
 2 ml Tel-E-Ject^(R) disposable syringes--boxes of 10 (NDC 0004-xxxx-xx);
 1 ml Tel-E-Ject^(R) disposable syringe cartridges--boxes of 10 (NDC 0004-xxxx-xx);
 2 ml Tel-E-Ject^(R) disposable syringe cartridges--boxes of 10 (NDC 0004-xxxx-xx).

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Stuart L. DuPen, M.D., Swedish Hosp., Seattle

and Martin P. McLaren, M.D., Assist. Prof. Anes., Howard Univ., Wash., D.C.

This was a double-blind comparison of midazolam hydrochloride and thiopental sodium for induction of anesthesia in unpremedicated patients. Eighty six patients participated and only one was excluded from analysis (induction failure in midazolam group, requiring intravenous fentanyl to complete induction). The dose of 0.3 mg/kg midazolam was administered over 5 seconds and two minutes was allowed for effect; 25% increments were administered every 2 minutes afterwards, if needed. The starting dose of thiopental was 4.0 mg/kg, in like fashion. The initial dose was re-evaluated serially during the study, and thus increased to 0.4 mg/kg midazolam hydrochloride solution after the first five patients in the McLaren study; there was also other leeway as manifested by initial midazolam dosage range of 0.26-0.5 mg/kg (initial thiopental dosage range was 3.79-4.23 mg/kg).

Of the 43 midazolam HCl patients for analysis, induction was successful in 40 cases. The mean dose in the successful cases was 0.37 mg/kg and the mean time was 121 seconds.

Of the 42 thiopental cases for analysis, induction was successful in 39 cases. The mean dose in successful cases was 4.2 mg/kg and the mean time was 85 seconds.

Midazolam patients took longer to awake, manifest orientation and to be discharged from the recovery room (spent more time in the recovery room) than did thiopental patients, but these differences were not clinically significant: midazolam hydrochloride patients were fit for discharge from the recovery room in a mean time of 95 minutes from entrance (median also 95 minutes) versus 72 minutes mean for thiopental (median 70 minutes). Time of surgery was a mean of 107.7 minutes (median 101 minutes) for midazolam HCl patients and a mean of 98 minutes (median 90 minutes) for thiopental Na patients. Choice of maintenance anesthetics would also effect recovery room stay but this information has not been analyzed; maintenance of anesthesia was left up to the investigators.

TABLE IV

RECOVERY FROM ANESTHESIA
(successful inductions only)

	Estimated Treatment Means	
	MIDAZOLAM (N=40)	THIOPENTAL (N=39)
Time to Awakening (minutes)	29.56*	17.90
Time to Orientation (minutes)	47.31**	27.08
Time Fit for Discharge (minutes)	95.16**	72.14

*Significantly longer than with thiopental (P < 0.05)

**Significantly longer than with thiopental (P < 0.01)

Acknowledgement is hereby made that the above table is from
NDA 18-654, Vol. 1.23, page 9ine.

page Two—Protocol 2213, pooled.

This study revealed no safety problems remarkable for induction of general anesthesia. One laryngospasm was noted on induction with midazolam, and it resolves spontaneously. Another laryngospasm (midazolam group) was noted during maintenance and responded to deepening of general anesthesia. Hiccoughs was noted during induction in one thiopental patient. Hive like wheal and flare was noted at the injection site in one midazolam patient and was attributed to allergic condition other than drug use ("asthma"). Pain on injection was noted in three midazolam and 9 thiopental treated patients. Five midazolam treated patients and four thiopental treated patients had one or more signs of venous irritation at postoperative evaluation; this is not unusual for indwelling intravenous lines for large volume parenterals but the investigators, since no other drugs were administered through the injection site in question, considered these venous irritations as possibly or probably drug related.

In 87.5% of the midazolam cases and 100% of the thiopental cases, there was no change in mean arterial pressure during induction of greater than 20%. Two midazolam patients manifested a mild decrease and two manifested a mild increase (same definition as before, 20-30% change); one midazolam patient manifested an increase of greater than 50% during induction (the summary does not provide more details except to note that management was accomplished by deepening of maintenance anesthetic).

There was no change of 20% or more in pulse rate during induction in 62.5% of midazolam patients and 74.4% of thiopental patients. Eight (20%) of the midazolam patients manifested a mild increase and 5 (12.5%) manifested a moderate increase, while 2 (5%) manifested a severe increase (greater than 50%, the summary does not provide more details). Three (7.7%) thiopental patients manifested a mild increase, 5 (12.8%) manifested a moderate increase and 2 (5.1%) manifested a severe increase. Management of severe changes was accomplished by deepening of maintenance anesthetic.

One patient took over 1 1/2 hours to become oriented after surgery. This was a male of about 50 years of age who underwent lumbar fusion. The institution in question (DuPen, et. al.) routinely lowers blood pressure by a moderate degree in such cases, in this case with Innovar, fentanyl, Mandol, propranolol and enflurane (dosages not provided). The patient did respond to commands at about the time of arrival in the recovery room but could not answer "Where are you?" for about another hour and a half. He spent two hours in the recovery room, which does not appear unusual to this reviewer and may even appear to be a short time considering the surgery. DuPen patient midazolam group, Vol. 1.170, Microfiche No. 106, Row A, Fiche 1, etc.

Hematological and biochemical screening, most determinations being conducted pre- and post-operatively in most patients, revealed no abnormalities reasonably associated with administration of either induction agent.

REVIEWER'S COMMENTS:

Induction is still slower than in actual anesthetic practice, but these data make a case for starting induction dosage of midazolam hydrochloride solution of about 0.35-0.4 mg/kg in unpremedicated patients. These data also suggest that recovery is slightly to moderately slower than is recovery from thiopental induction; this is subject to reservations discussed in the summary. The adverse observations are in keeping with induction and maintenance of general anesthesia; in the interest of brevity, some of the common respiratory depression problems that represent a pharmacologic response to all that is going on around the time of induction and maintenance of general anesthesia were mercifully left out of the safety review by me.

Protocol 2210

Z.W.Gramling, M.D., et. al., Medical College of Georgia, Augusta

This was a study of midazolam hydrochloride solution versus diazepam suspension for induction of general anesthesia in adult ASA Risk III patients. The study was ongoing at the time that the NDA was submitted, with analysis of the first 31 cases. Maintenance was according to clinician's choice. Assignment was randomized; the anesthesiologist monitoring the patient and gathering data afterwards was not aware of the test drug administered to particular patients. Patients were un-premedicated. Female patients predominated (about 75%).

The initial induction dose of midazolam HCl was 175 ug/kg, administered at a constant rate over 60 seconds. The protocol called for re-evaluation periodically of this dose, with the possibility of updating; after 5 midazolam cases, the initial induction dose was updated to 200 ug/kg. Increments of 25% were administered at a constant rate over 15 seconds every two minutes until satisfactory induction occurred. Induction was considered "unsuccessful" (for purposes of test drug study) if patients required additional agents for induction or if anesthesia lightened shortly after induction. In like manner, the initial induction dose of diazepam was 350 ug/kg; this dose was used for the first 10 cases and then it was updated to 400 ug/kg.

Induction was deemed successful with midazolam alone in 11/15 cases (73.3%), seven with the first dose and four after use of one 25% increment. The mean total dose of midazolam for induction was 211 ug/kg. The mean time to induction was 119 seconds.

Induction was successful with diazepam alone in 12/16 cases (75%), 10 with the first dose and two after use of one 25% increment. The mean total dose of diazepam for induction was 391 ug/kg. The mean time to induction was 95 seconds.

Awakening from anesthesia was rapid for both groups. The method of recording was different, with time of arrival in the recovery room as zero point. The diazepam patients were generally awake before arrival in the recovery room and the midazolam patients were generally awake about 5 1/2 minutes after arrival in the recovery room. The midazolam patients were judged fit for discharge from the recovery room in a mean time of 105 minutes after arrival and the diazepam patients were judged fit for discharge from the recovery room in a mean time of 115 minutes after arrival.

Eight diazepam and 4 midazolam patients manifested pain on injection of test drug. Phlebitis was reported in pt. (diazepam) and judged related to test drug administration. Vein induration, tenderness or redness, not severe enough to be judged phlebitis, was noted in another 4 diazepam patients and 3 midazolam patients (postoperative evaluation).

Most patients manifested no vital sign change greater than 20% during induction of general anesthesia; there were no severe changes. There seem to be, however, three cases of "bradycardia" that appear to be listed separately from pulse decreases. One of these (patient identified as diazepam group) is described as requiring atropine for management of bradycardia in the summary but there is no such information on the microfiche case report form; this is hardly worthy of additional pursuit.

One patient, a female of about 49 years, died 11 days after the study was conducted. This was patient _____ who received diazepam as test drug. She had metastatic cancer, otherwise not described, and surgery was an exploratory laparotomy. Secondary diagnoses were described as: Severe liver disease and malnutrition. Moderate lability of blood pressure was noted during surgery and this was treated with Wyamine and dopamine. From the available information on the case report forms, it appears that this was not unexpected; she recovered from these episodes, which were judged remotely (lowest available classification) related to test drug administration. Death was ascribed to generalized carcinomatosis, although the case report was filled out in advance of death. There seems no reasonable doubt about the ~~_____~~ clinical impression; I recommend that this cause of death be accepted.

Reviewer's Impression: This ongoing study suggests that the dose of midazolam for induction of anesthesia in ASA Risk III patients, unpremedicated, is approximately 200 ug/kg.

Whether officially recognized as an induction agent or not, diazepam is widely used for this purpose. My source is attendance at scientific presentations at medical meetings and noting published abstracts of same over the years. The replacement of water insoluble diazepam with water soluble midazolam may turn out to be a significant clinical advantage.

Median surgical time for Bivan's patients was approx. 73 minutes (mean app. 85 min.) and for Mahaffey it was app. 22 min. (mean app. 22.5 min.) with no significant drug treatment difference.

Protocol 2212A, pooled results

Hollis Bivens, M.D., M.D. Anderson Hospital (Cancer Hosp.), Houston, TX
and John E. Mahaffey, M.D., Med. Coll. South Carolina at Charleston

This was a comparison of midazolam hydrochloride and midazolam maleate, double-blind, in females with uterine carcinoma undergoing two treatments requiring anesthesia; most procedures were for insertion of irradiation material but there was no restriction and 4 patients underwent hysterectomies, etc. The study did not go quite as planned, in that 28 patients participated in the study but only 14 received both test drugs. The induction dose was 0.3 mg/kg, followed by a 2 minute wait and then 25% of the induction dose repeated every two minutes until satisfactory induction occurred. There was no premedication.

The study generally supported equipotency of midazolam maleate and midazolam hydrochloride in the 14 patients available for such comparison. The dose of 0.3 mg/kg was generally effective for both drugs (technically, mean midazolam maleate dose was 0.32 mg/kg and mean induction time was 104 seconds and mean midazolam hydrochloride dose was 0.31 mg/kg and mean induction time was 93 seconds). The mean time fit, after anesthesia and surgery, for discharge from the recovery room was 74 minutes for mid. mal. and 83 minutes for mid. HCl; keep in mind that agents selected for anesthesia have a significant impact on such results (these selections were left to the clinician and were not analyzed), as does anesthetic and/or surgical time.

Vital sign changes during induction were minor; 6.1% mean drop in mean arterial pressure for mid. mal. and 2.3% drop for mid. HCl, 0.7% mean pulse rate rise for mid. mal. and 8.0% rise for mid. HCl. Respiratory changes during induction are expected because of the variety of drugs used during early maintenance and for intubation, so these will not be discussed. The only significant adverse observation was a 30% incidence of self limiting hiccoughs during induction; pain on injection was noted in about 8% of the cases. One patient who received midazolam maleate in Dr. Mahaffey's study (#11) manifested agitation and excitation during emergence from anesthesia; it was impossible to communicate with the patient during this time; drug treatment included meperidine, naloxone and dopram and it was deemed successful; after such treatment the patient appeared comfortable and was judged coherent (there is not actually too much to be learned from the investigator's comments).

Hematological and biochemical screening, although very incomplete, revealed no trend of abnormal values reasonably associated with test drug administration.

SUMMARY: Midazolam maleate and midazolam hydrochloride solutions appear clinically equivalent in 14 patients who received both formulations at the initial dose of 0.3 mg/kg; the patients were unpremedicated. Total induction dose was close or identical to initial dose. Self limiting hiccoughs (30% of inductions) is the only side effect that bears watching.

Intravenous Induction Pooled Studies, Older Formulation of midazolam maleate.
(Premedication Studies 2089A, 2087A, 2088A, 2082A & 2090A)

D. Amaranth, Cleveland Clinic, 2089A, 33 patients/33 for efficacy analysis.
E. T. Finucane, Grady Hosp., Atlanta, and A.H. "Buddy" Giesecke, Dallas, 2087A,
101 patients combined/96 for efficacy analysis.
Raymond Miller, Mt. Sinai, NYC & L.H. Stehling, Syracuse Med. Cr., 2082A, 99 cases
combined/96 for efficacy analysis.
D. C. Hicks, St. Vincent's, NYC, 49 patients/44 for efficacy analysis, 2088A
A. F. Winnie, U. of Ill., Chicago, 2088A, 48 patients/47 for efficacy analysis.
William Murray, Duke, Durham, NC, 2090A, 48 patients/48 for efficacy analysis.

Also, Mali Mathru, Tulane, NO, LA, terminated after 13 cases, not pooled, insufficient
data for analysis of four groups. Investigator relocated. 2088A, morphine IM
premedication.

Gilbert Kinyon, M.D., Mercy Hosp., San Diego, 17 patients, 11 not evaluated
because of protocol violations. Sample too small for efficacy conclusion
based on analysis of four groups. Study was not pooled. 2089A, oral hydroxyzine
pamoate premedication.

SUMMARY: Anesthesia induction time was slowed down considerably from usual clinical
practice so that dose ranging could be conducted and so that the effects of premedication
(Innovar IM [a fentanyl-droperidol combination], hydroxyzine pamoate orally,
sodium secobarbital orally, morphine & atropine IM and oral diazepam) could be studied.
Premedication (all drugs except diazepam) promoted a greater percentage of successful
inductions, decrease^d induction drug requirements and shortened induction time.
This study suggests that it makes good sense to administer intravenous midazolam
for induction of anesthesia to premedicated patients and that there are a wide
range of premedicants to select from. Midazolam patients took a few minutes longer
to be considered worthy of discharge from the recovery room than did thiopental
patients, but the differences were not clinically significant.

METHOD:

Four hundred and seven adult surgical patients (general ^{operating} schedule) participated.
A total of 362 of these cases were included for analysis. Reasons for exclusion
included too long a time between premedication and induction of anesthesia, wrong
timing of test drug increments, maintenance agents started too early, discovered
alcohol and/or drug abuse, etc. The groups seemed comparable (mean age about
34 years, range 17-73 years but mostly under 60 years, about 2/3 female and
1/3 male, wt. about 68 kg mean, and all were ASA Status I or II).

These studies were relatively early in development of midazolam. Dosage started
at 0.15mg/kg and then quickly built up as analysis of data, performed after
every 12 cases (4 per group), suggested that larger initial doses were needed
(0.15-0.4 mg/kg). Thiopental initial dosage ranged between 2.5-4.5 mg/kg in the
same manner. The initial test dose was administered over about 30 seconds and
then 2 minutes was allowed for induction of anesthesia. Anesthesia was considered
successful if: 1. Eyelid reflex was lost, 2. If response to commands was lost, and
3. If there was loss of voluntary movement. If induction was not accomplished
within 2 minutes, 25% increments of test drug were administered over 5 seconds
and another 2 minutes allowed for drug action. This was repeated every 2 minutes
until induction was completed. The patients were randomly assigned to four
groups and the anesthesiologist monitoring patient during anesthesia, recovery
and the preoperative period was not aware of the test drug administered. Induction
was considered unsuccessful for the test drug if additional agents were required
for induction or if anesthesia lightened unduly following induction. Each
study had four groups: 1. midazolam maleate induction in unpremedicated patients,
2. midazolam maleate induction in premedicated patients, 3. thiopental sodium
induction in unpremedicated patients & 4. thiopental sodium in premedicated patients.

Premedications were as follows:

R. Miller & L. Stehling--Innovar (fentanyl and droperidol combination) 0.02 ml/kg IM one hour before induction or as close thereto as possible.

Brenda Finucane & "Buddy" Giesecke--Diazepam 10 mg orally, as close to 1 hour before induction of anesthesia as can be predicted.

L. Amaranth---Hydroxyzine pamoate 100 mg orally (Vistaril Capsules, Pfizer) one hour preoperatively or as close thereto as can be predicted.

Wm. Murray---200 mg of Sodium secobarbital orally (Seconal Caps, Lilly) as close as possible to one hour prior to induction.

R.G.Hicks and A.P.Winnie---Morphine sulfate 0.15 mg/kg IM and atropine sulfate 0.06 mg/kg IM, as close to one hour before surgery as can be predicted.

Excluded Studies--Dr. Mathru studied morphine sulfate without atropine and Dr. Kinyon studied hydroxyzine pamoate orally.

RESULTS:

	<u>Successful Induction</u> Total Pts. for Analysis (%)	Mean Total Dosage*	Mean Induction Time*	Mean Time Fit for Recovery Room Discharge*
Midazolam	45/91 (49.5%)	0.337 mg/kg	167 sec.	112 minutes
Midazolam plus premed.	66/89 (74.2%)	0.225 mg/kg	127 sec.	101 minutes
Thiopental	63/91 (69.2%)	3.79 mg/kg	123 sec.	85 minutes
Thiopental plus premed.	65/91 (71.4%)	3.43 mg/kg	105 sec.	95 minutes

*Successful Inductions Only

Results were consistent, except as follows: 1. Diazepam did not facilitate induction with thiopental and served only to decrease dosage of midazolam, but not time to induction, 2. In Dr. Winnie's study, dosage of induction agent, but not time to induction, was lessened by morphine premedication, 3. In Dr. Murray's study, time to induction was the same for midazolam alone and thiopental alone; the same was true for midazolam and secobarbital and thiopental and secobarbital. Only one of these requires a table:

B. Finucane and A.H.Giesecke, Diazepam Premedication Studies

	<u>Successful Inductions</u> Total Pts. for Analysis (%)	Mean Total Dosage*	Mean Induction Time*
Midazolam alone	9/24 (37.5%)	0.36 mg/kg	147 seconds
Midazolam and diazepam	13/26 (54.2%)	0.272 mg/kg	186 seconds
Thiopental alone	14/25 (58.3%)	3.851 mg/kg	103 seconds
Thiopental and diazepam *	11/26 (45.8%)	3.941 mg/kg	187 seconds

*Successful Inductions Only

midazolam maleate pre medication pooled (10), page 3hrs. —

SAFETY:

Pain on injection was noted in about 11% of midazolam patients and in about 8% of thiopental patients. There were no differences in evaluation of reaction at injection site; since this was via catheter and intravenous infusion left in place over time, no more need be said.

A scattering of mild to moderate changes in mean arterial pressure were noted around the time of injection with no difference between drugs except that two patients receiving thiopental manifested an increase in mean arterial pressure greater than 50% and there were no such cases for midazolam.

The same can be said for heart rate, except that five thiopental patients and only one midazolam patient manifested heart rate increase greater than 50%. The one case requiring additional comments will be handled below (Hicks # 41, thiopental group).

There was a difference in the incidence of hiccoughs, more common after administration of midazolam but usually self limiting. Hiccoughs were noted in 14 midazolam patients (14%), 8 midazolam plus premedication patients (8%), 3 thiopental patients (3%) and zero (0%) thiopental plus premedication patients.

Hicks patient No. 41, unpremedicated, received 220 mg of thiopental for ~~premedication~~ ^{induction on 29}. This was as 8.8 ml of 2.5% solution. The patient was a 29 year old female at that time, 62.8 kg, admitted for surgery of a neck mass, later cancelled. After induction, succinylcholine (quantity not stated) was administered; other drugs listed at about that time were 60 mg meperidine (presumably intravenously) and nitrous oxide 80% in oxygen. About 8 minutes after induction (my estimate from available information on Fiche # 227, Volume 1.171, Row B, No. 8) the patient developed hypotension (76/58) and afterwards developed a ventricular tachycardia at a rate of 250/minute. Treatment included intravenous fluids, intravenous lidocaine, intravenous propranolol, sublingual nitroglycerin, amyl nitrite inhalation, Aramine, phenylephrine, and later dopamine drip. Surgery was cancelled and the patient was taken to the recovery room, later to the Coronary Care Unit with a diagnosis of myocardial infarction. ^{October 1981.}

The discharge summary suggests that a diagnosis of non-transmural (subendocardial) myocardial infarction was made on the basis of: 1. Events following induction of anesthesia, 2. Appearance of ST & T changes on ECG taken 20 minutes later, 3. ST elevation in AVL, 4. Voltage decrease compared to admission ECG, 5. Later development of T wave inversions in I, AVL & V₆. Initially she tended to be hypotensive, blood pressure being maintained with dopamine. She soon stabilized and required no additional circulatory medication except for heparin. Atelectasis was noted and treated; pulmonary embolism was suspected but ruled out as a low possibility later. Enzymes were apparently not useful in establishing a diagnosis. Discharge was on 19 November 1981, with plans for a thorough evaluation of coronary circulation in 6-8 weeks. No medication was prescribed in the interim.

There is one confusing fact: The case report states that the patient was contacted by telephone at home seven days after induction of anesthesia, concerning localized side effects (pain, burning, redness at injection site, etc.). I cannot reconcile this with the rest of the history.

midazolam maleate premedication pooled (10), page 40u ---

Note that this case was in the thiopental control group (pre-1938 drug). Thiopental can hardly be blamed for the unfortunate chain of events but undoubtedly did contribute to the unexpected alteration in perfusion, leading to a later clinical diagnosis of subendocardial myocardial infarction.

REVIEWER'S COMMENTS:

Induction of anesthesia, for test purposes, was slower than that encountered in actual clinical practice. This should not detract from the observation that premedicated patients (almost any premedication tested, except possibly for 10 mg oral diazepam administered 1 hour before anticipated induction) required less induction agent (midazolam or thiopental) than did unpremedicated patients.

Protocol 2121, pooled summary

Wayne Porter, M.D., Dept. Anes., Brackenridge Memorial Hospital, Austin, TX
 John A. Reitan, M.D., Assoc. Prof. Anes., Univ. of Calif., Davis

This was a multi-center double-blind, randomized parallel-group comparison of midazolam hydrochloride solution and thiopental sodium solution for induction and maintenance of anesthesia; fentanyl 2 ug/kg was administered intravenously 5 minutes before induction of anesthesia. Procedures were brief, generally 20 minutes or less, with cystoscopy and dilatation and curettage predominating. Fifty six patients had participated at the time of NDA submission and the study was still ongoing at that time; there were 4 male patients and 52 female patients, all adults judged ASA risk status I or II. There were 46 successful inductions among the 56 patients and these cases were analyzed for induction (22 for midazolam and 24 for thiopental); most exclusions were due to starting nitrous oxide before induction of anesthesia was completed, even though inductions were thus successful. Patients who received drugs, such as analgesics or antiemetics, which might interfere with tests of recovery from anesthesia, etc., were excluded from that portion of the analysis.

Initial doses were 0.2 mg/kg midazolam and 3.5 mg/kg thiopental, administered over 30 seconds and then allowing 2 minutes for effect. If induction was not considered successful after two minutes, a 25% increment was administered over 5 seconds and this was repeated every 2 minutes if necessary; in actual practice, one increment sufficed in all but one case that was not induced successfully with the initial dosage. Initial dose was re-reviewed after every five cases, but in actual practice no dosage adjustment was deemed necessary. Induction was considered successful when the following three criteria were met: 1. loss of eyelid reflex, 2. loss of response to commands, 3. loss of purposeful movements in response to placement of the anesthetic mask. The anesthesiologist who administered the test drug knew which drug was administered but the anesthesiologist monitoring the patient during anesthesia was not aware of which test drug was administered; the anesthesiologist monitoring the patient in the recovery room and administering the psychomotor tests was not present in the operating room.

Maintenance of anesthesia was with nitrous oxide: oxygen 6 liters/minute: 3 liters/minute for five minutes then 4 l/m: 2 l/m for the rest of the case. No other gaseous or volatile liquid anesthetics were administered. Maintenance doses of 25% of the total induction dose of the test drug were administered intravenously when there were signs which the anesthesiologist judged attributable to light anesthesia: among the signs of light anesthesia watched for were movement, phonation, return of lid reflex, arrhythmias, tearing, sweating, coughing, swallowing, laryngospasm and increase in blood pressure or pulse rate.

Recovery from anesthesia was studied in detail. Patients were judged to have awakened when they were drowsy but now able to respond to simple verbal commands. Patients were judged oriented when they could answer three simple questions (1. Name?, 2. Date of birth?, 3. "Where are you?"). Psychomotor tests were performed before test drug administration and serially after orientation for 24 hours: 1. Hand coordination was measured by number of pegs turned on a peg board in 30 seconds, 2. Vigilance was measured by the ability to connect dots arranged in rows (not Treiger Test), 3. Time needed to place six differently shaped blocks in appropriately shaped holes, 4. Ability to repeat digits read in a series, starting with four and going as high as nine.

Impairment of Recall: Retrograde amnesia and anterograde amnesia were tested as follows:

Protocol 2121, page 2wo--

Prior to test drug administration, patients were shown a picture of a large dollar bill ("memory card"). In the recovery room, when oriented, patients were shown and asked to identify pictures of 10 common objects. At the 24 hour post-anesthetic visit, these pictures were presented again, intermingled with 10 additional pictures and the memory card; patients were asked to identify those pictures seen previously. Retrograde amnesia was judged present if the patient failed to recognize the "memory card". Anterograde amnesia was considered total if no pictures were recalled, partial if one to four pictures were recalled, and absent if five to ten pictures were recalled.

RESULTS:

All of the tables reproduced in "RESULTS" are from NDA 18-654, Volume 1.31.

<u>TABLE II</u>		
INDUCTION OF ANESTHESIA†		
	MIDAZOLAM (N=22) Initial Dose 0.20 mg/kg ††	THIOPENTAL (N=24) Initial Dose 3.50 mg/kg ††
Success of Induction		
Initial Dose	17	23
1 increment	4	1
2 increments	1	0
Mean Total Induction Dose (mg/kg)	0.21	3.52
Mean Time to Induction (seconds)		
Initial Dose	81	49
1 increment	191	110
2 increments	200	-
Mean Total Time to Induction	106**	54

**Significantly longer than with thiopental (P < 0.01)

†Excludes patients who received N₂O prior to successful induction

††Doses reflect a ± 0.02 mg/kg range in starting dose for midazolam and a ± 0.35 mg/kg for thiopental.

Addendum to Table II: Additional inspection of printouts reveals that the maximum time to induction was 270 seconds (Porter) for midazolam hydrochloride solution and 110 seconds (Reitan) for thiopental sodium solution.

TABLE III

DRUGS ADMINISTERED DURING MAINTENANCE OF ANESTHESIA

	N	Mean Dosage		Mean Duration of Surgery (minutes)
		Test Drug (mg/kg)	Fentanyl (ug/kg)	
MIDAZOLAM	23	0.18	1.16	20
	2	0.13	-	28
	1	-	0.36	11
	2	-	-	15
THIOPENTAL	23	2.79	0.68	23
	1	2.00	-	54
	1	-	0.50	21
	2	-	-	14

TABLE IV

RECOVERY PARAMETERS†

	Estimated Geometric Means	
	MIDAZOLAM (N=25)	THIOPENTAL (N=24)
Time to Awakening (minutes)	21.20**	10.37
Time to Orientation (minutes)	27.44**	10.96

**Significantly longer than with thiopental (P < 0.01)

† Excludes patients who received sedatives in recovery room

TABLE V

ANALYSIS OF PSYCHOMOTOR TEST RESULTS AND DROWSINESS

Percent of Patients Estimated to be at Baseline Level:	Time (minutes) to Return to Baseline Levels						Significance of Chi-Square*
	MIDAZOLAM (N=25)			THIOPENTAL (N=24)			
	25%	50%	75%	25%	50%	75%	
No. of Pegs turned in 30 seconds	87	203	322	61	132	294	N.S.
No. of Dots crossed correctly†	120	190	341	58	86	148	P<0.01
No. of Blocks inserted	63	122	239	50	145	329	N.S.
No. of Digits repeated correctly	27	65	122	16	30	69	N.S.
Drowsiness	41	54	100	18	28	36	P<0.01

*Significance indicates shorter times with thiopental

†Midazolam N=24, Thiopental N=23

TABLE VI

ANALYSIS OF AMNESIA PARAMETERS

	N	Retrograde Amnesia		Anterograde Amnesia		
		Present	Absent	None	Partial	Complete
Midazolam	24	2	22	0	4	20**
Thiopental	26	1	25	13	3	10

**Significantly more (P<0.01) complete anterograde amnesia with midazolam (83%) than thiopental (38%)

Significantly more (P<0.01) complete or partial anterograde amnesia with midazolam (100%) than thiopental (50%)

SAFETY: No ventilatory problems unusual for induction and maintenance of general anesthesia were noted. Two of Porter's patients manifested partial laryngospasm following induction with midazolam, managed in the usual manner (in this case ventilatory control; no muscle relaxants are mentioned in the summary); one of these also manifested hiccoughs lasting one minute during maintenance of anesthesia. Venous irritation of some sort was noted postoperatively in 14.3% of midazolam patients and 10.7% of thiopental patients; remember that large volume parenterals were employed, mostly through 18 Gauge catheter at the wrist or hand area.

One midazolam patient manifested moderate decrease (20-30%) in mean arterial pressure during induction; the rest manifested no change (16 or 76.2%), meaning less than 20%, or mild decrease (3 or 14.3%) or mild increase (1 or 4.8%). The mean change from

Protocol 2121, page 5ive—

minus 7.37 mmHg for midazolam and minus 4.36 mmHg for thiopental. Results for thiopental are comparable to those of midazolam.

Pulse rate changes during induction were comparable between thiopental and midazolam, meaning no change greater than 20% in about 85% of the patients in each group and a scattering of mild and moderate changes in the others, except for one severe increase (greater than 50%) in one thiopental patient. ~~This patient is not identified~~
~~_____~~ Mean pulse rate change for midazolam patients was minus 4.36 beats per minute and mean pulse rate change for thiopental was plus 1.30.

SUMMARY: For adult surgical patients who receive 2 ug/kg fentanyl intravenously five minutes before induction of general anesthesia, the dose of 0.2 mg/kg midazolam or slightly more will usually suffice for induction. Induction is relatively rapid, generally in less than two minutes, but not as rapid as for thiopental. The combination of incremental doses of fentanyl and midazolam during surgery, for brief surgical procedures such as dilation and curettage, when combined with nitrous oxide in oxygen, will provide satisfactory maintenance of anesthesia that cannot be accounted for by the presence of subpotent nitrous oxide alone. Time to awaken after this regimen is about 21 minutes and time to orientation is about 30 minutes; awakening and orientation following a thiopental-fentanyl regimen took about 10 minutes (awakening) and 11 minutes (orientation). This difference should not be ignored but it also should not pose unusual patient management problems. Psychomotor tests, after orientation, were comparable for the two groups except that thiopental patients were able to connect dots properly faster than were midazolam patients, no big deal. Neither drug was associated with retrograde amnesia; midazolam was associated with complete anterograde amnesia, under the conditions of testing; in 20/24 patients (83.33%), partial anterograde amnesia in 4/20 patients (16.67%) and no anterograde amnesia in no cases; thiopental was associated with complete anterograde amnesia in 10/26 cases (38.5%), partial anterograde amnesia in 3/26 cases (11.5%) and no anterograde amnesia in 13/26 cases (50%). Clearly, the regimen of midazolam and fentanyl impaired recall more than did the regimen of thiopental and fentanyl. Neither agent posed unusual safety problems for induction of anesthesia.

Pooled Protocol 2066E

Albert Shih, M.D., Anes. Dept., New Jersey Medical School, Newark
Yung-Fong Sung, M.D., Assist. Chief to Director of Anes., Emory Univ., Atlanta

Eighty adult surgical patients, ASA Status I & II, participated in a double-blind, randomized parallel study of induction with midazolam hydrochloride or thiopental sodium after being premedicated with 1 mg/kg of meperidine IM and glycopyrrolate 0.005 mg/kg IM. Patients were selected on the basis of surgery anticipated in advance to last approximately 90 minutes or less. In practice there were 78 female patients and 2 male patients, although there was no sex restriction or specified surgery; gynecological surgery tended to predominate but other procedures, such as rhinoplasty, breast biopsy, etc., were also included. One patient was excluded from analysis because pre-anesthetic medication had been administered about two hours before the actual time of induction of anesthesia. Another patient was excluded from evaluation of venous irritation, only, because the patient received steroids during maintenance of anesthesia. Blinding was in that the anesthesiologist monitoring the patient during anesthesia, recovery and postoperatively was not aware of the test drug administered. In actual practice premedication varied minimally from the planned dosage, suggesting some patient individualization (actual dosage of meperidine, for instance, was in the range of 0.75-1.04 mg/kg but usually approximately 1 mg/kg). Patient groups were comparable as to age, weight and race distributio

The induction dose of test drug was administered over 20 seconds and 2 minutes was allowed for effect: starting dose of midazolam was 0.2 mg/kg and for thiopental it was 3.5 mg/kg; the protocol called for re-evaluation of dosage after each 12 completed cases but this did not occur regularly so that results heavily reflect an initial dose of 0.2 mg/kg midazolam. If induction was not complete in 2 minutes, 25% increments were administered over 5 seconds and another 2 minutes allowed until satisfactory induction occurred with 25% increments. Maintenance anesthesia, after induction was completed, was with nitrous oxide, oxygen and enflurane. If these agents were added before induction was completed, induction was labeled as unsuccessful (for the test drug). As before, induction of anesthesia was considered complete when there was loss of lid reflex, loss of response to commands and loss of purposeful movement in response to placement of the mask.

RESULTS:

Under the conditions of this investigation, anesthesia was induced with a mean total dose of 0.276 mg/kg midazolam hydrochloride in a mean time of 119 seconds. A mean total dose of 3.963 mg/kg thiopental was employed to induce anesthesia in a mean time of 82 seconds. Keep in mind the slower, dose-ranging, requirements of the protocol as contrasted to generally more rapid administration of induction agents (or at least willingness to offer the patients additional increments at a faster rate) in actual clinical practice, even in academic institutions.

Most of what can be learned from this study regarding efficacy and recovery from anesthesia can best be learned from the tables reproduced on the following pages & derived from pages 8, 9 & 10 of Volume 1.25, NDA 18-654:

TABLE II
SUCCESS OF INDUCTION

	MIDAZOLAM (N=38)		THIOPENTAL (N=41)	
	N	%	N	%
Successful induction	34	89.5	38	92.7
Unsuccessful induction†	4	10.5	3	7.3

†Patients required an additional agent for induction or anesthesia lightened following induction

TABLE III
INDUCTION OF ANESTHESIA†

	MIDAZOLAM			THIOPENTAL	
	Initial Dose (mg/kg) 0.20 (N=22)	0.30 (N=6)	0.40 (N=6)	Initial Dose (mg/kg) 3.5 (N=22)	4.0 (N=16)
No. Increments Required					
0	15	3	5	17	15
1	6	3	1	3	0
> 1	1	0	0	2	1
Mean Time to Induction (seconds)					
Initial Dose	73	118	100	58	61
1 increment	188	176	180	173	-
> 1 increment	274	-	-	236	228
Mean	114	147	113	90	71
Mean Total	119			82	
Mean Total Dose (mg/kg)	0.220 0.335 0.321			3.338 4.134	
Group Mean Total Dose	0.276			3.963	

† Successful inductions only (patients did not require additional agents for induction or anesthesia did not lighten following induction)

Doses reflect a : 0.05 mg/kg range in starting dose for midazolam and
a : 0.25 mg/kg range in starting dose for thiopental

TABLE IV
RECOVERY FROM ANESTHESIA
(successful inductions only)

	Estimated Treatment Means	
	MIDAZOLAM (N=34)	THIOPENTAL (N=38)
Time to Awakening (minutes)	28.03**	15.82
Time Fit for Discharge (minutes)	84.52	79.32

**Significantly longer than with thiopental (P < 0.01)

Duration of anesthesia (nitrous oxide, oxygen & enflurane) was a mean of 99 minutes and a median of 93 minutes for midazolam patients and a mean of 78 minutes (median 84 minutes) for thiopental patients. This must be considered when evaluating the above table, but by now these results seem consistent between studies (recovery from immediate effects of anesthesia is slightly to moderately faster when patients receive thiopental for induction instead of midazolam).

SAFETY:

There were no drug differences in vital sign changes during induction of anesthesia. In about 88% of the cases there was no change of greater than 20%. There was no mean arterial pressure change greater than mild (20-30%), and then only in one midazolam patient. There was no heart rate change greater than a moderate increase (30-50%), and then only in one thiopental patient (no midazolam patients).

TABLE VIII
VITAL SIGN CHANGES FROM
BASELINE TO IMMEDIATELY POST INDUCTION
(successful inductions only)

	N	Estimated Treatment Means			
		Mean Arterial Pressure (mm Hg)		Pulse Rate (beats/minute)	
		Mean Change from Baseline	Mean Immediately Post Induction	Mean Change from Baseline	Mean Immediately Post Induction
MIDAZOLAM	34	-7.88**	82.53	-0.11	89.10
THIOPENTAL	37	-5.45**	85.81	1.12	92.04

**Significant change from baseline (P < 0.01)

Pain on injection was reported for 1 midazolam patient. Swelling or redness of the vein on postoperative evaluation was noted in 2 midazolam patients and 4 thiopental patients. Keep in mind that an indwelling catheter and large volume parenteral administration is involved with the injection site.

Apnea at the time of induction was noted in about 62% of cases for each drug tested. This is not unusual from the combination of agents administered shortly after induction

Pooled Protocol 2066E--page 4our---

and from the tendency of anesthesiologist to assist or control ventilation in all patients. Hiccoughs was noted in one thiopental patient and in zero midazolam patients.

SUMMARY:

In this controlled clinical investigation, with patients premedicated with approximately 1 mg/kg meperidine and 0.005 mg/kg glycopyrrolate, the mean induction dose of midazolam hydrochloride solution was 0.276 mg/kg, in the mean induction time of 119 seconds. The mean induction dose of the comparative drug, thiopental sodium solution, was 3.963 mg/kg, in a mean time of 82 seconds. Awakening was faster for thiopental patients, a fact which should be considered but which would usually be of little or no clinical significance and may sometimes actually be desirable; discharge from the recovery room was also faster for thiopental patients but only by about 5 minutes, a really insignificant figure. Mean surgical time was 93 minutes for midazolam patients and 78 minutes for thiopental patients; anesthesia consisted of nitrous oxide, oxygen and enflurane. There were no unusual safety problems revealed by this study.

Keep in mind that induction of anesthesia under actual clinical circumstances would tend to be somewhat faster or at least there would be readiness to add additional induction drug faster than under the artificially slow circumstances needed to gather data in this and similar protocols.

Fragen, et. al., Protocol 2192.

This was a study of two groups of ASA I & II female patients undergoing brief gynecological procedures under general anesthesia, for a total of 24 patients. The first group was called the "younger" group, aged 18-30 years (n = 12). The second group was called the "older" group, aged 49.75 to 60 years (n = 12); the intent was to include ages 50-60 in this group, but one slightly younger patient altered the range a tiny bit.

Five minutes prior to induction of anesthesia, fentanyl was administered intravenously in the dose of 1.5 ug/kg. Midazolam 200 ug/kg was employed as a single dose for induction, administered intravenously over 30 seconds; this dose sufficed in all patients.

Maintenance was with nitrous oxide in oxygen, supplemented with 50 ug (1 ml) of fentanyl when the patient appeared lighter (opened eyes, phonated or responded to command); anesthesia was very light.

Treiger test was performed as for Protocol 2085A (Fragen). Street fitness was as for Protocol 2085A, and so was impairment of recall testing. In short, everything except test drug administration was as for 2085A.

RESULTS:

Induction was accomplished in a mean of 65.4 seconds in the "younger" group (range 45-90 seconds) and in a mean of 61.7 minutes in the "older" patients (range 35-95 seconds). This difference was not judged statistically significant, and is not of practical significance.

Duration of anesthesia varied, mean 21.8 minutes in the "younger" group and 15.2 minutes in the "older" group. Eight "young" patients received fentanyl during maintenance (6-one dose & 2-two doses); the mean total for these patients was 1.07 ug/kg fentanyl. Four "old" patients required fentanyl during maintenance (3-one dose & 1-two doses); the mean total for these patients was 1.11 ug/kg. This difference in patients requiring supplemental fentanyl was not judged statistically significant. I would also like to note the duration difference which could explain this.

"Older" patients took longer to awake than did "younger" patients. After that, there was not much difference, as the table below (page 267 of Volume 1.28 of the NDA) will show:

RECOVERY FROM ANESTHESIA

RECOVERY TIMES (minutes)	Adjusted Means	
	MIDAZOLAM "Young" (N=12)	MIDAZOLAM "Old" (N=12)
Awakening	8.09*	22.58
Orientation	23.61	36.56
Fit for Discharge (Street Fitness)	72.63	79.29
Ability to Stand	53.27	64.90
Ability to Walk	72.84	77.33
Baseline Treiger* Competency	96.80	123.00

*p < 0.05

*Excludes 3 patients (2 young and 1 old) whose scores did not return to within two dots of control until the day after surgery and 1 old patient who did not perform the tests.

One "young" patient manifested mild drowsiness at 6 hour postoperative evaluation. No patients were drowsy at 24 hour evaluation and all could walk steadily without assistance. The "older" patient who did not perform the Treiger Test was unable to do so without her glasses and they were not available.

No patient had retrograde amnesia. In the "younger" group, 4 patients had partial amnesia (defined in Protocol 2085A summary) and the other 8 patients had total amnesia. In the "older" group, one patient had partial amnesia and the other 11 had total amnesia.

Hiccoughs were observed in one "old" patient during maintenance and another during recovery. One "young" patient also manifested hiccoughs during recovery. In the opinion of the investigator, these observations were possibly drug related.

Tenderness at the infusion site was noted in four patients (redness on only one of these). All of these lesions disappeared within a week of surgery. In one of these cases, the intravenous site was already sore before test drug administration. Relationship to test drug administration in these cases was considered possible in all cases.

during induction

Vital sign changes were minimal in this study, none greater than 20% in most cases; the only exception was a 30-50% decrease in heart rate in two of the "young" patients.

REVIEWER'S COMMENTS: It has been suspected for years that age made a difference in response to some of the benzodiazepines. In these two relatively young groups of patients, one older than the other, subtle differences were manifested, always in favor of earlier recovery in the younger of the two groups. Awakening time² was statistically significant, but later measures of recovery were not.

Under the conditions of this experiment, maintenance requirements may be greater in the younger group but these differences (number of patients requiring supplementation for these short procedures) could also be accounted for by the different duration of anesthesia. No big deal in any case!

With regard to use of midazolam, fentanyl and nitrous oxide for short surgical procedures in female patients, it can be concluded that: 1. younger patients awaken faster, 2. after awakening, no other clinically or statistically significant differences in recovery measurements were shown in this relatively intense evaluation of recovery, 3. drug use as in this investigation need not be modified because of age, over the age range of 18-60 years at least.

These data also support the dose of 200 ug/kg (0.2 mg/kg for induction of anesthesia in patients who have first received 1.5 ug/kg of intravenous fentanyl, 5 minutes before induction of anesthesia.

Roy Cronnelly, Protocol 2254

Dr. Cronnelly is one of the better known members of the muscle relaxant research team in the Anesthesia Department of the Univ. of Calif., San Francisco.

This study was ongoing at the time of NDA submission and the following information is derived from the first 14 of 20 planned cases. The study, first of all, establishes clinical compatibility of midazolam with the non-derolarizing neuromuscular blocking agent, pancuronium. The study also suggests a clinically insignificant degree of drug interaction, which in the opinion of this reviewer could be accounted for by chance and individual patient variation alone.

The patients were all adult good risk elective surgical patients. Premedication consisted of 1 mg/kg meperidine IM about 1 hour before induction of anesthesia. Patients were randomly assigned to receive a single induction dose of either midazolam 300 ug/kg or thiopental 4 mg/kg, total over 20 seconds, for induction of anesthesia. All inductions took place within 2 minutes, but time of induction was otherwise not recorded.

Patients were connected to neuromuscular monitoring equipment in the standard manner. Supramaximal single twitch response was recorded by polygraph and verified by electromyograph (stimulation of the ulnar nerve at the wrist). Immediately after induction, baseline twitch response was determined. Then increments of pancuronium were administered in the dose of 25 ug/kg until approximately 99% depression of twitch response was achieved. Maintenance anesthesia consisted of nitrous oxide and oxygen.

RESULTS:

Some patients required 2 doses of pancuronium and some patients required 3 doses:

50 ug/kg produced 99% blockade in 5/7 midazolam patients and 1/7 thiopental patients (2 increments of 25 ug/kg each).

75 ug/kg produced 99% blockade in 2/7 midazolam patients and 6/7 thiopental patients (3 increments of 25 ug/kg each).

Mean doses were: midazolam patients (n = 7) 57 ug/kg
thiopental patients (n = 7) 71 mg/kg

The mean duration, 99% blockade to 10% blockade (89% recovery), was 95 minutes in the midazolam patients and 85 minutes in the thiopental patients. Median duration was 85 minutes in the midazolam patients and 83 minutes in the thiopental patients.

midazolam
SAFETY: one patient manifested what is simply described as a hive-like elevation along the vein following induction. This lasted for one hour and was considered possibly related to test drug administration. There is some question that this same patient may have previously manifested such a reaction to intravenous administration of meperidine; the investigators conclude that this is more likely related to the administration of meperidine.

REVIEWER'S COMMENTS:

There is a great deal of patient variation in correlating specific doses of muscle relaxants with particular degrees of blockade. There were only two doses to choose from (2 increments or 3 increments of 25 ug/kg each). What was really sought was the minimum dosage for near 100% blockade, since exactly 99% is unattainable. It so happened that the minimum dosage turned out to be less in the midazolam patients, but it could have just as easily been the other way around. More important, the midazolam patients received more muscle relaxant but recovery was not prolonged. I see no clinically significant drug interaction here.

Roy Cronnelly, M.D., Univ. of Calif., S.F., Protocol 2255

Dr. Cronnelly is one of the better known members of the neuromuscular blockade research team of UCSF, formerly directed by R.D. Miller, M.D., who is now Chairman of the Dept. of Anesthesia.

This was a randomized study of succinylcholine interaction with midazolam 300 ug/kg for induction (n = 10) or thiopental 4 mg/kg for induction (n = 10). Both drugs were administered for induction over 20 seconds and anesthesia induction was complete within 2 minutes in all cases. Precise times of induction were not recorded. Premedication, about 1 hour before induction, consisted of meperidine 1000 ug/kg IM or IV.

The ~~supramaximal~~ single twitch response of the adductor pollicis muscle to supramaximal ~~stimulation~~ ulnar nerve stimulation at the wrist was recorded by polygraph and verified by electromyography, in the usual manner. This was done, baseline, immediately after induction and then followed serially after intravenous administration of 1000 ug/kg succinylcholine.

Anesthesia was maintained with nitrous oxide and oxygen.

RESULTS:

Duration of blockade, from administration of succinylcholine until twitch had returned to 90% of control value, did not vary between the two groups, lasting about 9 minutes in each case.

Rate of recovery, from the time when first twitch reappeared until it was 90% of control value, did not vary between the two groups, lasting about 3 1/2 minutes in each case.

REVIEWER'S COMMENTS:

Most inductions are performed with thiopental. Most endotracheal intubations are performed in patients under the influence of succinylcholine, being short acting for the most part. Thus these two drugs are very commonly used together near the beginning of general anesthetics. These data suggest that there is no difference in the action of succinylcholine if induction is with midazolam instead of thiopental.

I have also reproduced, on the next page, a table from the sponsor's summary. This table provides more information on mean, median and range for DURATION OF BLOCKADE & RATE OF RECOVERY. Note also that both polygraphic determinations and EMG were made and that the results follow each other closely (a few seconds apart).

Cronnelly, 2255, page two of summary.

<u>TABLE II</u>		
NEUROMUSCULAR TRANSMISSION		
	<u>MIDAZOLAM</u> (N=10)	<u>THIOPENTAL</u> (N=10)
<u>DURATION OF BLOCKADE (seconds)</u>		
Thumb Adduction		
Mean	541	545
Median	560	567
Range	270-650	400-650
Electromyography		
Mean	572	595
Median	593	630
Range	260-710	390-780
<u>RATE OF RECOVERY (seconds)</u>		
Thumb Adduction		
Mean	216	212
Median	205	218
Range	135-360	150-270
Electromyography		
Mean	248	260
Median	235	278
Range	130-360	150-420

Protocol No. 2139B, Philip Lebowitz, M.D., Anes., Mass. Gen. Hosp., Harvard Univ.

This was a double-blind (third party) randomized comparison of midazolam hydrochloride 0.15 mg/kg (n = 9) and thiopental 3 mg/kg (n = 11) for hemodynamic effects in patients judged ASA III. The patients mainly underwent peripheral vascular surgery (one had renal artery stenosis, but there appear to be no other diagnoses which might upset the circulatory results; this patient was in the midazolam group) but there were also several burn grafts, etc. Patients with New York Heart Assn. Classifications II through IV were excluded from this study. Patients were not on chronic cardiac medication (as were patients in Reves 1092A & 1092, previously summarized); they were usually on some concomitant antibiotic therapy, perhaps prophylactically. Male patients predominated (81%). Patients were selected for participation in this study if they required some kind of arterial and central venous catheter because of the elective surgical procedure under consideration.

In actuality 21 patients participated. Patient ^{very} became agitated after injection of test drug midazolam and thiopental was used to manage this problem. This patient was excluded from analysis and replaced by another patient. The next patient was assigned by the randomization code to receive thiopental, thus there are more cases of thiopental for analysis than there are cases for midazolam (9 versus 11).

Premedication: Morphine sulfate, dose individualized (0.04-0.15 mg/kg), intramuscularly; the plan was to administer this one hour before anticipated induction of anesthesia but in actuality the time range varied from 24-120 minutes. After arrival in the anesthesia induction room, additional morphine (0.06-0.2 mg/kg) was given intravenously for sedation prior to placement of the central venous catheter and arterial catheter. Patients were given nitrous oxide in oxygen (4:2 l/minute) to inhale by mask. At this point patients were still arousable and breathing spontaneously.

When stable baselines for sedation and cardiovascular measurements were attained, the test drug was administered over 30 seconds. As patients lost consciousness, ventilation was assisted to maintain PaCO₂ at approximately 40 mmHg.

Serial measurements consisted of: Mean arterial pressure (MAP), Mean right atrial pressure (MRAP), Heart rate (HR), Cardiac output (CO) (by indocyanine green technique using 5 mg of dye injected into the central venous circulation and computerization of radial arterial indocyanine). Calculated measurements were: Stroke volume (SV) and Systemic vascular resistance (SVR). The units for SVR were different than in the Reves studies:

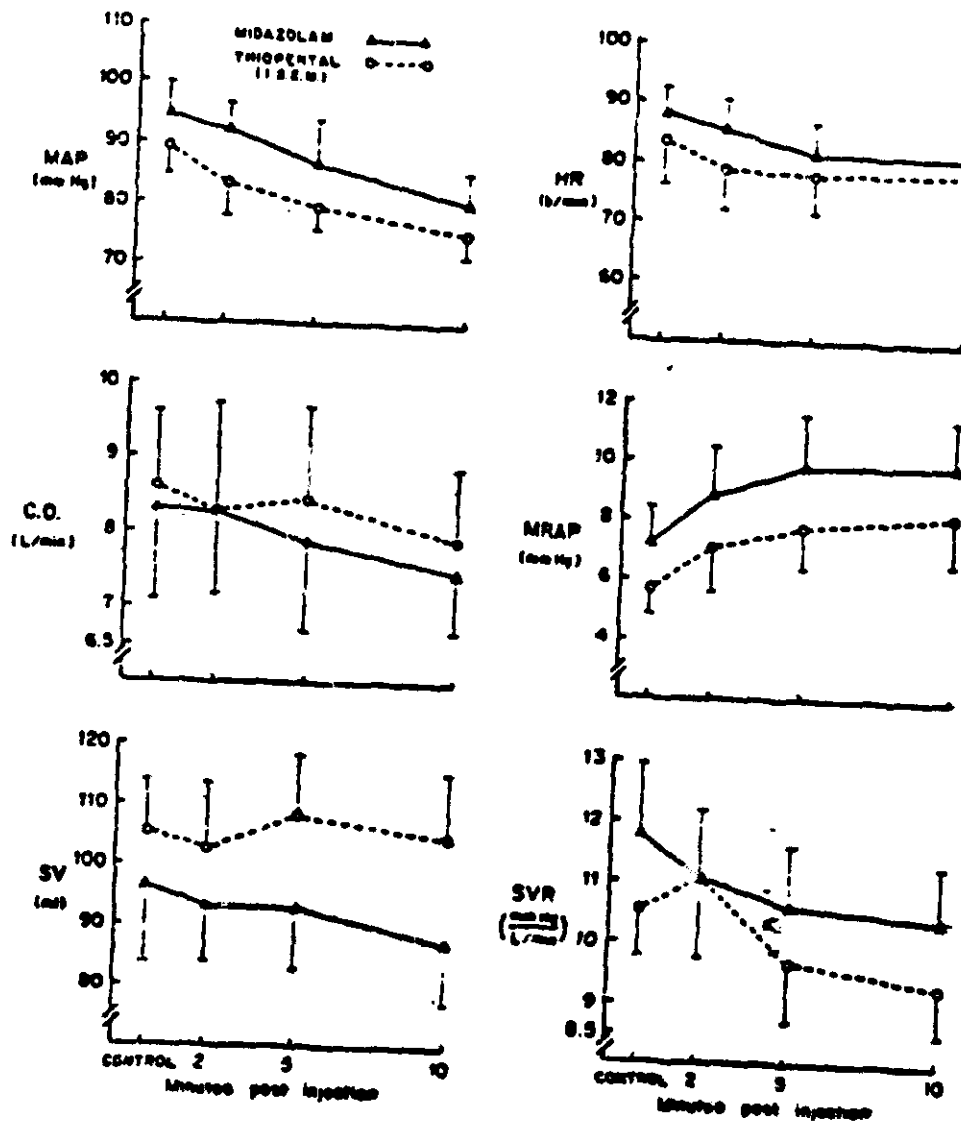
$$SVR \text{ (mmHg/l/min)} = \frac{MAP - MRAP}{CO \text{ (l/min)}}$$

There were no other drugs and no surgical stimulation during the 10 minutes of data gathering which followed test drug administration.

Doses of test drug were in keeping with the protocol, with minimal variation range. Anesthesia was induced in 94 seconds (range 20-510) for midazolam and 32 seconds (range 10-65 seconds) for thiopental (median for midazolam was 40 seconds and for thiopental was 30 seconds). There were several minor protocol errors in the patients included for analysis: 1. Two midazolam patients unintentionally received midazolam maleate which had been shipped for another study; the dose was correct and these patients were not excluded from analysis. 2. One thiopental patient did not receive intravenous morphine because no peripheral line was available (the study drug was later given by central venous catheter); this patient did receive IM morphine 0.149 mg/kg approximately 1 hour before placement of the central venous catheter.

Circulatory results can best be appreciated from Figure - 1. This figure is from the sponsor's summary (page 144 of Volume 1.33).

Figure - 1



SAFETY: There were no severe vital sign changes during the 10 minute test period.

The case of severe agitation involves a relatively young (about 48 years old) man with peripheral vascular disease and impending gangrene of the right leg, scheduled for aorto-femoral bypass graft; he weighed 70 kg. He did not go to sleep after receiving test drug midazolam and became extremely agitated. This was quickly managed with thiopental and there were no additional problems. The patient had no recollection of this adverse experience when interviewed afterwards; it is specifically noted that he suffered no ill effects. This was judged severe and "possibly" related to test drug administration.

Another patient, extremely apprehensive before induction, went in and out of sleep during the ten minute test period, as determined by return of lid reflex and minimal response to voice. Midazolam group.

Another patient became hypotensive after surgery and this was attributed to blood loss during surgery. This was successfully managed with albumin and packed red blood cells.

Four midazolam patients and eight thiopental patients manifested brief episodes of apnea associated with induction. Some were managed with assisted respiration and some were so transient that they resolved spontaneously. This is expected in anesthesia and is easy to manage by properly trained personnel.

REVIEWER'S COMMENTS:

This was a different patient population than Reves 1092A & 1092, previously summarized. Reves patients had myocardial ischemia and were mostly on propranolol and coronary vasodilators. These patients had peripheral vascular disease (most patients) but were not on propranolol and vasodilators. Thus we see different heart rates to start with and a different response to test drug administration. The Reves patients tended to have slow heart rates to begin with (55-65 per minute) and heart rates rose slightly after test drug administration. These patients had faster heart rates to begin with (83-88 per minute) and heart rates fell slightly after test drug administration.

Both investigators used morphine before test drug administration. Some Reves patients received nitrous oxide before test drug administration and some didn't. All of these patients received nitrous oxide. We must consider this study as a study of the circulatory effects of midazolam (or thiopental) in ASA Status III patients premedicated with morphine and also receiving inhalational nitrous oxide 67%.

In both Reves studies and this study myocardial oxygen demand-supply ratio (indirect estimate) appears favorable.

Study No. 2139

Philip Lebowitz, M.D., Anes., Harvard Univ. & Mass. Gen. Hosp., Boston.

This was a comparison of cardiovascular effects of 0.25 mg/kg midazolam maleate and thiopental 4 mg/kg, administered intravenously over 30 seconds for induction of general anesthesia in patients judged ASA CLASS I or II who were scheduled to undergo elective surgery of a kind for which arterial and central venous catheters would ordinarily be placed.

Methodology was virtually identical with the methodology for Study No. 2139B, previously summarized. This was a double-blind (third party) randomized parallel study. Premedication, also like 2139B, was with morphine sulfate IM about 1 hour (range 25-137 minutes) before entering the anesthesia room; doses were individualized, ranging between 0.06-0.14 mg/kg. Another dose of morphine was administered intravenously in the anesthesia room prior to placement of the previously cited invasive monitoring equipment. Nitrous oxide 67% in oxygen was also started about this time. Direct and calculated circulatory data was determined as for 2139B. No other manipulation or drugs were allowed during the 10 minutes of data gathering after test drug administration.

Twenty one patients participated, with data for twenty cases analyzed (in one case direct measurements only were analyzed---see below); data were analyzed for 11 midazolam cases and 9 thiopental cases. Ages were comparable (mean 45.4-46.3 years---range 24-68 and 29-62---figures for midazolam first). Surgery consisted of a variety of thoracic procedures, peripheral vascular procedures, hip prosthesis revision, upper and lower gastrointestinal procedures, etc.; groups seem matched in terms of the severity of the situation requiring elective surgery, generally pretty severe. There was no pattern of chronic medication. PaCO₂ was kept at approximately 40 mmHg during the test period.

RESULTS:

Patient _____ was excluded from analysis. This patient was extremely apprehensive (56 y. male with scheduled aorto-femoral bypass graft). Blood pressure had been 130/80, on hydrochlorothiazide, but it jumped to 150/90 during preparation for test drug administration. Cardiac output could not be satisfactorily performed 2 minutes after test drug administration because the patient developed airway obstruction (managed with an oropharyngeal airway and repositioning) and moved. This patient was in the thiopental group. All other measurements were taken over the 10 minute period, including cardiac output at times other than 2 minutes. This patient was ~~apparently~~ deleted and replaced at a later date by patient _____ from analysis who was randomized to receive midazolam, thus accounting for the differing number of patients in each group; it is not clear who decided to replace this patient.

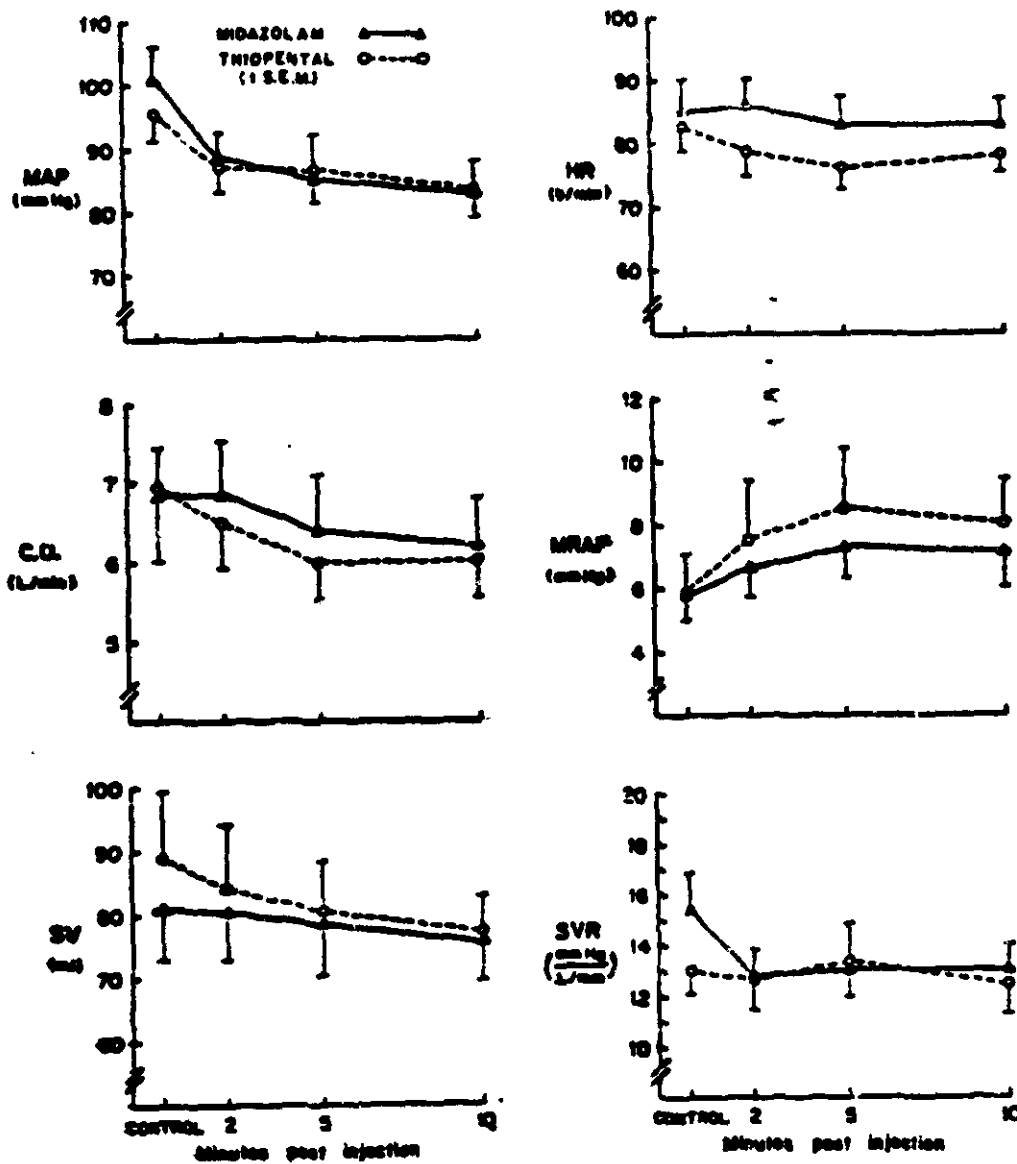
Patient _____ was included for direct measurements only. The arterial line malfunctioned and never did work right. Systemic arterial pressures were measured, instead, by sphygmomanometer. Cardiac output could not be determined and thus calculated measurements could also not be determined. This patient received thiopental. Thus we have mean arterial pressure and heart rate for 9 thiopental patients but cardiac output, stroke volume & systemic vascular resistance for only 8 thiopental patients. It is not clear to this reviewer why this patient was not also excluded from analysis???

One patient exceeded the planned 65 year age limit by 3 years, but was not excluded from analysis. This seems o.k. One patient seemed very excitable, so the investigator did not wait until baseline measurements were stable for 10 minutes before administering test drug. An evaluation of the case report form makes it appear that it was a good idea to go ahead and induce anesthesia rather than risk renewed excitement, labile elevation of blood pressure and pulse, etc. This patient was included for analysis and there seems to be no real reason not to have.

For the record I should also note that, while checking some of the case reports for other reasons, I noted ~~fluctuation~~ lability of blood pressure (mild to moderate elevation of an intermittent nature) in some patients while receiving invasive monitoring; ~~fluctuation in blood~~ pulse rises in the 120/minute range were also commonly noted at the same time. I did not notice all of this for 2139B, in patients judged to be sicker (ASA Status III). The patients in 2139 were probably healthier and many were probably apprehensive about the rapidly approaching extensive surgery. These measurements generally came back down during the ten minutes allowed for ~~same after placement of invasive monitoring.~~

Circulatory results can best be understood from Figure 1, derived from page 176 of Volume 1.33, NDA 18-654:

Figure 1



This was no special study of induction time, but 19 of the 21 patients were asleep in a mean of 31 seconds after midazolam administration (range 3-60 sec.) and a mean of 24 seconds after thiopental administration (range 15-35 seconds). Patient is one exception; patient _____ (midazolam) was also hard to get asleep.

Study No. 2139, page 3hree----

SAFETY:

Four midazolam patients and 8 thiopental patients manifested brief periods of apnea associated with induction. Some were so transient as to be allowed spontaneous resolution and others were managed with assisted respiration. This is so common during induction of anesthesia, and so routinely managed by trained anesthetist, as to not deserve special mention.

Patient _____ (midazolam group) manifested postoperative hemorrhage for 3 hours, which responded to transfusions. Some minor S-T segment changes were noted on ECG postoperatively, presumably at this same time. These were not observed before or during anesthesia. Baseline pattern returned by the next ECG, 24-36 hours later. It is the opinion of this reviewer that this adverse experience is not reasonably associated with administration of test drug.

There were no severe changes in vital signs from baseline after test drug administration (the ten minute test period); baseline here means after the patients stabilized following intravenous morphine and placement of invasive monitors (except in one case, previously cited, ten minutes of stability was allowed before test drug administration).

No venous irritation was noted.

REVIEWER'S COMMENTS:

Consider the results in the light of morphine premedication, both IM and IV, and with intercurrent use of nitrous oxide 67% (N₂O:O₂ ratio of 4L/2L per minute). Midazolam and thiopental were associated with decrease in MAP, HR, C.O., SV & SVR; MRAP rose slightly. The peripheral changes would suggest favorable oxygen demand-supply ratio by indirect estimate; of course, these patients were not plagued by symptomatic coronary artery disease.

I can't figure out why patient _____ was not excluded from analysis, being that patient _____ was excluded from analysis.

These patients seemed more apprehensive about impending surgery than did patients in Lebowitz Study No. 2139B; 2139B patients were generally sicker. This could explain greater lability of blood pressure and pulse (upward direction) while the patients were being prepared for test drug administration. These measurements generally calmed down by the time of test drug administration.

Note the contrast with Reves 1092 & 1092A, where the pulse tended to rise slightly after test drug administration. Reves patients were generally on propranolol and coronary vasodilatory, for the treatment of myocardial ischemia, and had slow heart rates to begin with (55-65/minute).

Joseph G. Reves, M.D., Univ. of Alabama, Birmingham, Protocol 1011
Dr. Reves is well known for his knowledge about clinical management of patients undergoing anesthesia for cardiopulmonary bypass.

This was a study of use of midazolam maleate or thiopental for both induction and maintenance during a variety of scheduled surgical procedures. Fifty ASA Risk I & II patients, mostly female, participated. Two midazolam patients and 5 thiopental patients were excluded from analysis for a variety of technical violations and another 3 patients were excluded because test drug received could not be definitively ascertained from the records. This left 20 patients per group for data analysis. The study was double-blinded in that the person gathering data did not know which group the patients were assigned to.

Premedication consisted of atropine 0.006 mg/kg and morphine 0.1 mg/kg IM, 1-2 hrs. before surgery. For all practical purposes, the dose of midazolam maleate was 200 ug/kg, administered intravenously over 5-10 seconds (mean-204 ug/kg, median-200 ug/kg), with this dose sufficing for induction of general anesthesia. The dose of thiopental was 3 mg/kg, and this also sufficed. N2O/O2: 4/2 L/min. was administered.

For maintenance: 13/20 patients for analysis in the midazolam group also received midazolam during maintenance. Increments were 1/3 of the induction dose, up to 3 such doses. The mean maintenance dose for these 13 patients was 130 ug/kg total (median-130 ug/kg, range 70-210 ug/kg). Two patients required supplementation with non-protocol agents such as droperidol, enflurane or halothane. The mean duration of anesthesia was 59 minutes. Need for supplementation was based on judgement that tachycardia, increased blood pressure, diaphoresis

15 Fifteen of 20 patients in the thiopental group received maintenance thiopental in the same manner. The mean total dose was 2.11 mg/kg, median 1.92 mg/kg, range .99-7.72 mg/kg. Three patients were excluded from analysis because they required non-protocol agents, as above. The mean duration of anesthesia was 68 minutes.

Patients also received small doses of non-depolarizing muscle relaxants prior to first administration of succinylcholine (standard to subdue fasciculations) for intubation. Subsequent relaxation was provided by succinylcholine drip. Narcotics were not used during induction. (Summary Table B-3 and spot check of case report forms). It seems valid to conclude that anesthesia was accounted for by the morphine premedication and by the test drug administration. Obviously, succinylcholine could have provided for lighter anesthesia but would not have masked tachycardia, increased blood pressure and perhaps other signs of lightening of anesthesia. The investigator team has kept this research into maintenance of anesthesia about as simple as is possible, since one drug cannot be used alone for what is today regarded as safe general anesthesia.

Time to awakening was a mean of 7.5 minutes (range 3-20 minutes) in the midazolam group and 5 minutes (range 1-24 minutes) in the thiopental group. Time to orientation (name, place, date & approx. time) was a mean of 43 minutes in the midazolam group (range 6-92 minutes) and a mean of 36 minutes in the thiopental group (range 6-99 minutes). Emergence was judged smooth in all cases (not rated in 1/20 midazolam patients) where emergence was rated.

There were no specific tests of impairment of recall, other than memory of basic perioperative events before and after test drug administration (such as, "do you remember getting on the operating table" & "do you remember waking up in the recovery room"). The results of these crude questions did not support retrograde or anterograde amnesia.

f/or movements were due to lightening of anesthesia.

or maintenance

some

balanced

Reves, # 1011, page two--

Most patients in both groups manifested no change greater than 20% in calculated mean arterial pressure during induction. The same is true of heart rate, but two patients in the midazolam group did manifest severe increase (greater than 50% or required treatment).

REVIEWER'S COMMENTS:

These data support the induction dose of 200 ug/kg midazolam in patients premedicated with 0.1 mg/kg morphine IM. These data also support use of midazolam for support of anesthesia in procedures lasting up to about one hour. Generally several drugs are used per patient for support of anesthesia. Here we have simply morphine premedication, test drug administration, nitrous oxide in oxygen for maintenance and use of succinylcholine (with some of its side effects subdued by various non-depolarizing muscle relaxants); this is about as simple as you can get testing for maintenance of balanced anesthesia. The fact that two cases required non-protocol agents is not surprising. Those who evaluate efficacy of anesthetic agents are used to 100% efficacy but this situation is different; 15/20 patients required supplementation during maintenance and in 13/15 cases (86.6%) the midazolam sufficed. This reviewer is convinced that midazolam and the comparative drug, thiopental, made a contribution to maintenance.

Awakening and orientation testing showed that gross recovery from thiopental was shorter than gross recovery from midazolam, by now a consistent observation in these summaries. In this case, the time differences were not of clinical significance.

Study Protocol No. 2085A

Robert J. Fragen, M.D., Northwestern Univ., Chicago.

ASA Status I & II

This was a clinical investigation in 100 female patients, aged 19-60 years, who were scheduled for surgical procedures judged in advance to take 40 minutes or less. Under double-blind conditions, induction and maintenance was compared in four groups, blinded in that the person recording data was not aware of test drug administration:

1. n = 25. Premedication, about 5 minutes before induction, was with 1.5 ug/kg of fentanyl intravenously. Induction was with 175-250 ug/kg midazolam. If induction was not accomplished within 2 minutes, increments of 25% were administered every 2 minutes until satisfactory induction was achieved.
2. n = 25. Same use of fentanyl as above, Thiopental 3.5-4 mg/kg for induction 5 minutes later; 25% increments, if needed, as above.
3. n = 26. Saline instead of fentanyl. Midazolam as above.
4. n = 24. Saline instead of fentanyl. ~~Midazolam~~ Thiopental as above.

When anesthesia lightened, maintenance doses of test drug (midazolam or thiopental), 25% of induction dose, were administered. If patients could not be maintained in this manner, enflurane was added (n = 5) and these cases were excluded from evaluation of maintenance but not induction. and recovery

Serial Treiger Tests (sequence of dots to be joined after sufficient practice) were performed baseline and every 15 minutes after orientation until the patient was judged "street fit" (not drowsy, conversed normally, fully oriented to time and place, walked steadily without assistance and had stable vital signs) and later at 6 and 24 hours postoperatively. The critical measurement (time of critical value) was judged to be when the number of dots missed was within two dots of control.

Memory card was shown at the time of baseline Treiger Test (big dollar bill). When oriented, the patients were shown pictures of and asked to identify 10 common objects. At the 24 hour anesthesia visit, these pictures were again shown, intermixed with 10 additional pictures of common objects and the memory card. Retrograde amnesia was judged present if the patient failed to recognize the memory card. Anterograde amnesia was considered total if no pictures were recalled, partial if 1-4 pictures were recalled and absent if 5-10 were recalled.

Vital sign changes were classified as before. The vein and IV site were examined 24 hours and 1-2 weeks postoperatively for signs of phlebitis.

RESULTS:

Exclusions: One patient developed a perforated uterus and a laparoscopy was necessary. Anesthesia was continued with other agents. There were no postoperative complications. This patient was excluded from all efficacy analysis. Four midazolam without fentanyl patients and one thiopental without fentanyl patient required enflurane for maintenance of anesthesia and were excluded from evaluation of maintenance and recovery; they were, however, included in analysis of efficacy of induction. All of this seems proper to this reviewer.

The mean duration of anesthesia was approximately 17 minutes for each group. Surgery was mainly gynecological, with dilatation and curettage predominating.

2985A, page two---

Midazolam without fentanyl---18/26 cases were induced with the first dose, mean of 230 ug/kg. but, 14/17 who received an initial dose of 230-260 ug/kg required no increments. Mean total induction dose was 260 ug/kg. The mean time of induction in patients who did not require increments was 83 seconds (range 73-90 seconds and 230-260 mg). One increment sufficed in 6 cases requiring increments; five increments were administered to one patient with a starting dose of 192 ug/kg; four increments were administered to one patient with a starting dose of 229 ug/kg.

Midazolam with fentanyl 1.5 ug/kg---23/25 were successfully induced with a mean dose of 176 ug/kg midazolam intravenously, without increments. The mean total dose in this group was 180 ug/kg. The mean induction time in these 23 patients was 67 seconds (range 60-68 seconds). Four increments were required in one patient who received an initial dose of 161 ug/kg midazolam and one increment was required in one patient who received an initial dose of 184 ug/kg. The sponsor's summary states that a dose of approximately 160-200 ug/kg midazolam appears to be sufficient to induce sleep in premedicated patients. Technically, I would qualify this to state that this dose appears sufficient to induce sleep in patients premedicated with 1.5 ug/kg fentanyl intravenously, 5 minutes before induction of anesthesia. Other studies, however, testify to the efficacy of most premedicants tested.

Thiopental without fentanyl---23/24 were successfully induced with 3.68-4.23 mg/kg thiopental in a mean time of 55 seconds.

Thiopental with fentanyl 1.5 ug/kg---25/25 were successfully induced with thiopental in the single dose range of 3.51-3.95 mg/kg in a mean time of 36 seconds, measured as usual for this study by loss of lid reflex and loss of response to placement of the anesthetic mask.

Overall, anesthesia was successfully induced in all 99 cases that were subject to analysis, 89 with the first dose and 10 with incremental supplementation (most commonly one supplementation, equivalent to 25% of initial dose).

The following table, from page 178 of Volume 1.28 of the NDA, gives a breakdown of initial doses for patients who were successfully induced with the initial dose:

INDUCTION DOSE AND TIME TO INDUCTION
Induction with Initial Dose

Test Medication (mg/kg)	No. Pts.	Mean Time to Induction (seconds)	Test Medication (mg/kg)	No. Pts.	Mean Time to Induction (seconds)
<u>MIDAZOLAM</u>			<u>MIDAZOLAM + FENTANYL</u>		
0.175	1	68	0.175	20	68
0.200	3	80	0.200	3	60
0.225	4	73			
0.250	10	90			
Mean			Mean		
0.234	18	83	0.176	23	67
<u>THIOPENTAL</u>			<u>THIOPENTAL + FENTANYL</u>		
3.5	12	55	3.5	15	36
4.0	11	55	4.0	10	37
Mean			Mean		
3.8	23	55	3.7	25	36

Maintenance: Maintenance, without enflurane, was successful in 94/99 cases. This means that incremental doses of the test drug were administered, if needed, and that anesthesia otherwise consisted of nitrous oxide in oxygen. Patients treated with midazolam alone required more maintenance drug than did patients treated with midazolam plus fentanyl (9 ug/kg/minute versus 5 ug/kg/minute). This should all be clear from the table reproduced below (from page 179 of Volume 1.28 of the NDA):

MAINTENANCE OF ANESTHESIA
Maintenance Dose (Mean ± S.D.)

	MIDAZOLAM (N=22)	MIDAZOLAM + FENTANYL (N=25)	THIOPENTAL (N=22)	THIOPENTAL + FENTANYL (N=25)
Total Dose (mg/kg)				
Mean	0.15 ± 0.10	0.08 ± 0.06	3.64 ± 1.95	1.70 ± 1.25
Median	0.13	0.07	3.37	1.17
Dose per minute (mg/kg)	0.008 ± 0.007*	0.005 ± 0.005	0.213 ± 0.104**	0.099 ± 0.072
Ratio (total maintenance as percent of induction dose)	56.82 ± 34.9	40.2 ± 30.7	95.67 ± 51.9	45.42 ± 33.6
Ratio per minute (maintenance dose per minute as percent of induction dose)	3.57 ± 2.5***	2.55 ± 2.9***	< 5.6 ± 2.7	2.64 ± 1.9***

*Significantly greater than midazolam plus Fentanyl (p=0.02, t-test)
**Significantly greater than thiopental plus Fentanyl (p<0.01, t-test)
***Significantly lower than thiopental (p<0.01, analysis of variance)

In a general way, the investigator suggested from his comments that this type of anesthesia was light anesthesia. Fourteen midazolam patients phonated, moved and/or wiggled during the procedure, whereas only two midazolam plus fentanyl patients did so. This also testifies to such use of fentanyl.

and drug effects upon recall

RECOVERY: Recovery time measurements should be clear from the tables reproduced at the top of the next page, from pages 181 & 182 of Volume 1.28 of the NDA. Note also that no patient manifested retrograde amnesia. Midazolam appears to act independent of fentanyl in partial and total anterograde amnesia; since there is a mixture of cases involving partial amnesia and total amnesia, the term "---impairment of recall" comes to mind. Thiopental was associated with less impairment of recall than was midazolam.

Note that awakening was slower for midazolam, but that the times were clinically insignificant. Other measurements of recovery also favored thiopental, but patients were generally fit for discharge in less than two hours for all groups.

RECOVERY FROM ANESTHESIA

Recovery Times (minutes)	Midazolam (N=22)	Midazolam + Fentanyl (N=25)	Thiopental (N=22)	Thiopental + Fentanyl (N=25)
Awakening	14.44**	12.05	5.70	7.31
Orientation	49.93**	37.85*	14.67	13.31
Fit for Discharge	108.75*	80.34	53.37	94.31
Ability to Stand	87.69**	70.74	43.85	57.11
Ability to Walk	108.12**	79.73	52.06	64.91
Baseline Trieger Competency [†]	124.99**	103.70*	33.46	73.32

*p <.05 versus thiopental

**p <.01 versus thiopental

*p <.01 versus thiopental plus Fentanyl

†Excludes 7 patients whose scores did not return to within 2 dots of control until 24 hours post surgery and 1 patient whose score had not yet returned at 24 hours.

ANTEROGRADE AMNESIA

	Total Pts.	Degree of Amnesia					
		None		Partial		Total	
		N	%	N	%	N	%
Midazolam	21	3	14.3	5	23.8	13	61.9
Midazolam + Fentanyl	25	2	8.0	9	36.0	14	56.0
Thiopental	22	15	68.2	7	31.8	0	0.0
Thiopental + Fentanyl	25	16	64.0	6	24.0	3	12.0

SAFETY:

The majority of patients manifested no change in mean arterial pressure greater than 20% during induction of anesthesia (92-100%, depending on the group). The same is true for pulse rate during induction (75-83%). Most vital sign changes were mild to moderate as previously defined. The one exception is that two thiopental patients manifested a pulse rate increase greater than 50% (defined as severe increase); since this was not seen with midazolam or midazolam with fentanyl, the case reports were not inspected.

Hiccoughs were observed in 7 midazolam patients, 1 midazolam plus fentanyl patients and 2 thiopental patients. Drug relationship was considered probable or possible by the investigator. These appear to have been self limiting.

Pain on injection was reported by two midazolam and one thiopental treated patients. Vein irritation was observed in 7 midazolam, 5 midazolam plus fentanyl, one thiopental and two thiopental plus fentanyl patients. Timing is not stated in the summary, but these were obviously postoperatively; the lesions were judged to be due to mechanical irritation or extravassation and only possibly drug related. I would tend to agree, based on experience with indwelling catheters. This seems to have posed no long term patient management problems.

based on information gathered from patients

Subjective

A Drowsiness: Drowsiness is not unusual during recovery from anesthesia and in the postoperative period that follows, however, the investigator's comments in this regard are more thorough than most and deserve citing. Patient (midazolam) stated she "just can't wake up" at the 6 hour evaluation. Patient (midazolam) reported a "drugged" feeling more than with previous anesthetics. These two were considered adverse experiences. The following comments were also made, although not considered adverse experiences:

- Pt. (midazolam) - Persistent fatigue the next day.
- Pt. (midazolam) - "Spacey" in Recovery Room.
- Pt. (midazolam) - More drowsy than on previous occasions.
- Pt. (midazolam with fentanyl) - Fatigued the day of surgery and on awakening the next day.
- Pt. - For 6 days patient felt "not as sharp" mentally as she was used to feeling.

Objective Drowsiness: Investigators also noted that one midazolam patient manifested mild drowsiness at 6 hours after surgery; at the same time of evaluation, another patient manifested mild drowsiness plus inability to walk steadily. All patients could walk steadily without assistance and were judged objectively free of drowsiness at the time of 24 hour evaluation.

The sponsor's summary also lists respiratory depression typical for induction of anesthesia. This is so common, and so routinely managed by those administering anesthesia, as to not deserve citation in this review. Apnea was least common For Instance: after midazolam alone (2 cases, 7.7%) and next least common after midazolam plus fentanyl (11 cases, 44%); these observations lasted from 20-60 seconds. Apnea was noted in 54.2% of thiopental cases for from 15-120 seconds, as well as in 72% of the thiopental plus fentanyl cases for from 20-240 seconds. For other respiratory observations, if needed, see pages 182-184 of Volume 1.28 of the NDA.

REVIEWER'S COMMENTS: Initial induction dose did vary, but none of the initial doses appear high. After reading this, I would recommend that the anesthesiologist consider administering 1.5 ug/kg of intravenous fentanyl 5 minutes before induction of anesthesia and that under such circumstances an initial dose of about (+) 0.2 mg/kg intravenous midazolam be considered. This is a little higher than the mean effective dose reported in this study; the onset of this drug is somewhat slower than the onset for thiopental; too long an induction, if routine, would tire the patience of most surgeons. Without premedication, higher doses of around (±) 0.3 mg/kg would seem more appropriate. Again, this is slightly higher than the mean dose employed in this study, for the same reason.

The data also support use of midazolam to supplement subpotent anesthetics (nitrous oxide in oxygen) ^{meaning} for maintenance of anesthesia in short surgical procedures. Dose per minute is lower if intravenous fentanyl is administered, 1.5 ug/kg, five minutes before induction.

Recovery is faster in those cases where fentanyl was employed as above. As for the other studies reviewed to date, recovery is slower in the midazolam patients than in the thiopental patients, but not enough to preclude use of midazolam. Note especially that these experienced investigators judged patients fit for discharge in all groups within less than two hours.

I see no remarkable safety problems. Drowsiness, subjective and objective, was noted at followup interviews for some midazolam patients but no thiopental patients. Hiccoughs, apparently self limiting, was more common in midazolam patients.

Venous irritation is as expected following use of indwelling catheters, but still it was more commonly observed in midazolam patients, perhaps a chance happening.

Protocol 1092A

Joseph G. Reves, M.D., Univ. of Alabama, Birmingham.

This was an open study of hemodynamic changes after intravenous induction with midazolam maleate or diazepam in 30 patients undergoing elective myocardial revascularization. The patients were well matched into three groups, however, there was no randomization; one group was started and the next group was started when the first group finished (10 patients), etc. Mean age was about 55 years for each group and each group was 80-100% male; median weight was 81-86 kg (range 47-104 kg):

1. Premedication in all groups consisted of morphine and scopolamine IM, doses individualized. The intent was to administer this 60-90 minutes before induction of anesthesia; I checked some case reports for another reason (to be discussed later in this review) and those which I checked had 120-135 minutes between premedication and induction of anesthesia.
2. Ten patients received 100% oxygen by mask ^{before} being induced with midazolam maleate, during induction and during gathering of immediately post induction data. The dose of midazolam maleate for induction was 0.2 mg/kg and the mean induction time was 28 seconds (loss of eyelid reflex and loss of response to oral commands), median time also 28 seconds.
3. In like manner, ten patients received 50% oxygen and 50% nitrous oxide during the gathering of pre-induction data, during induction and during gathering of immediate post induction data. The dose of midazolam maleate was 0.2 mg/kg and the mean induction time was 23 seconds (median = 23 seconds).
4. As an afterthought, another group was added by the investigator, to receive 100% oxygen as above and induction with diazepam 0.5 mg/kg (n = 10). The median time for induction was 36 seconds and the mean time was 38 seconds.
5. Prior to induction, patients were prepared with catheters in two peripheral veins, radial artery and pulmonary artery (Swan-Ganz triple lumen thermodilution catheter inserted via the right internal jugular vein). Serial direct measurements included: ECG, heart rate, mean arterial pressure, systolic and diastolic systemic pressure, mean pulmonary arterial pressure, pulmonary arterial pressure systolic and diastolic, pulmonary capillary wedge pressure, cardiac output (thermodilution) and arterial blood gases. From these data, derived measurements were calculated, including cardiac index, stroke index, rate pressure product, and left ventricular work index (the last two judged to be indications of myocardial oxygen demand versus supply).
6. About 4-5 minutes after induction, pancuronium 0.1 mg/kg was administered to achieve neuromuscular blockade for endotracheal intubation. Upon completion of the blockade the trachea and laryngeal area was sprayed with 4 ml of 4% lidocaine and the patients were intubated.
7. During cardiopulmonary bypass, the induction dose of test drug was again administered to determine the effect on systemic vascular resistance of this dosage during bypass. It is not clear from the summary, case reports or protocol what drugs were used during this stage of maintenance of anesthesia. It is clear that para-induction and intubation testing was with light anesthesia as noted above but this would obviously not be adequate for the surgery itself.

RESULTS:

The circulatory results can best be seen from the figures, derived from the sponsor's summary (in Volume 1.34), reproduced on the next several pages. An important consideration for myocardial revascularization is that injection of midazolam and diazepam was accompanied by a moderate drop in mean arterial pressure and a moderate rise in heart rate; the net result was a drop in rate-pressure product, suggesting favorable ratio of myocardial oxygen demand as related to supply. The left ventricular stroke work index also fell.

Serial arterial blood gases confirmed that hypercapnia and hypocapnia did not develop during the test period, that pH remained in normal range and PO₂ was in keeping with oxygen delivery noted and satisfactory ventilation.

Note that heart rates were slow to begin with; the majority of patients were chronically on propranolol (19 of 30) and preparation for surgery seemed geared towards avoiding agents which might accelerate heart rate.

Other chronic medications include isosorbide dinitrate (22/30) and nitroglycerin (14/30).

The administration of pancuronium was accompanied by a mild to moderate increase in heart rate, in keeping with the clinical pharmacology of pancuronium. Midazolam induction, at least under this light general anesthesia, offered no protection against this effect of pancuronium. In addition, intubation under light general anesthesia caused additional acceleration in heart rate.

Safety:

Three midazolam plus 100% oxygen patients manifested what the summary describes as a "severe" increase in heart rate around the time of induction. Two diazepam and oxygen patients had the same adverse observation entered. In addition, one of the midazolam plus oxygen patients who manifested a "severe" increase in heart rate also manifested a "severe" increase in mean arterial pressure during this same test period. These observations made it seem necessary to check the case reports to complete my evaluation. All of these adverse observations looked quite different after conducting such an evaluation; the timing of all vital sign measurements were precisely noted, as were induction times, time of administration of pancuronium and time in relation to endotracheal intubation. It was obvious from the case reports that these accelerations in heart rate were related to endotracheal intubation, or rather endotracheal intubation under very light general anesthesia. It is the opinion of this reviewer that there was no reasonable association with test drug administration.

Seven out of 10 diazepam patients manifested pain on injection of study drug and there were no such adverse observations for midazolam patients. These observations appear to have been short lived.

One patient in the midazolam plus oxygen group manifested bronchospasm during induction. The patient was a male, about 69 years of age. Other drugs to watch in patients with bronchospastic tendencies included the morphine premedication and chronic administration of propranolol. The case report notes that there was no bronchospastic problem attributed to use of propranolol; the same appears true for the morphine premedication. Temporally, all that is clear from the case report (patient _____) is that bronchospasm, judged mild and self limiting,

developed after the induction of anesthesia with 0.2 mg/kg midazolam. After the study period, diphenhydramine 50 mg was administered intravenously and halothane was added. Some improvement was noted but the patient still manifested a prolonged exhalational phase. The reporting clinician felt that there was a "remote" possibility that this adverse experience was due to administration of test drug. The patient had no chronic pulmonary disease by history but he had been a heavy smoker in the past before quitting 12 years earlier; the clinician felt that pulmonary disease had not been ruled out (still, preoperative PaCO₂ was 36 mmHg and subsequent measurements were below the hypercapneic range; PaO₂ was also satisfactory during the test period). Much of this is reconstructed from the case report form, there being no detailed account in the summary, and allowance has to be made for a handwriting that is illegible at times. It is the opinion of this reviewer that no incrimination of midazolam as being capable of precipitating bronchospasm should be made on the basis of this case alone but must be based upon the overall application.

Patient also manifested a transient "severe" drop in mean systemic arterial pressure about the time of induction. No treatment was required and this was judged "remotely" related to test drug administration (lowest available classification on check list). Perhaps this was associated with the bronchospasm and/or chronic medication. My impression is that this drop in blood pressure is not reasonably associated with administration of midazolam. A "moderate" decrease is also checked off after intubation, also transient.

Patient (a 52 year old male, 75 kg, on metoprolol, hydrochlorothiazide, Isodil & nitroglycerin) manifested moderate systolic hypertension preoperatively (150/65-185/80 range) with some suggestion of lability. Mean systemic blood pressure changed the 108 range preoperatively to a low of 53 (80/40) 4-5 minutes after induction with midazolam 15.2 mg (about 200 ug/kg). This was judged "severe" but transient, and did not require treatment. Beyond that, I can't say much.

ROCHE was asked by me to help locate "severe" decreases in mean arterial systemic pressure around the time of induction of anesthesia. They could come up with only three cases, all for midazolam. This includes the two cases cited above and patient in Fragen Study No. 830A.

REVIEWER'S COMMENTS:

Use of midazolam for induction of anesthesia in patients undergoing myocardial revascularization does not appear to be associated with unfavorable indirect estimate of the ratio of myocardial oxygen demand to supply. Blood pressure were fell slightly and pulse rate increased slightly. Pulse rates slow to begin with and the majority of patients were chronically on propranolol. Midazolam did not protect against the tendency of pancuronium to elevate pulse rate. These patients were very lightly anesthetized during the test period and frequently the added stimulation of endotracheal intubation produced elevation in blood pressure and pulse rate; this observation does not appear to be reasonably associated with test drug administration.

One case of bronchospasm is reported. Midazolam should not be incriminated on the basis of this case.

Two cases of "severe" mean systemic blood pressure drop are reported around the time of induction of general anesthesia. There is only one other such case reported in this NDA (induction studies). One case does not appear reasonably associated with test drug administration.

The drug can't be incriminated in the other case either based on a suggestion of labile systolic hypertension under treatment and a scarcity of similar cases. These observations were transient and did not require treatment.

Those who wish to make additional deductions from this circulatory research are invited to view the figures on the next several pages (copied from the sponsor's summary).

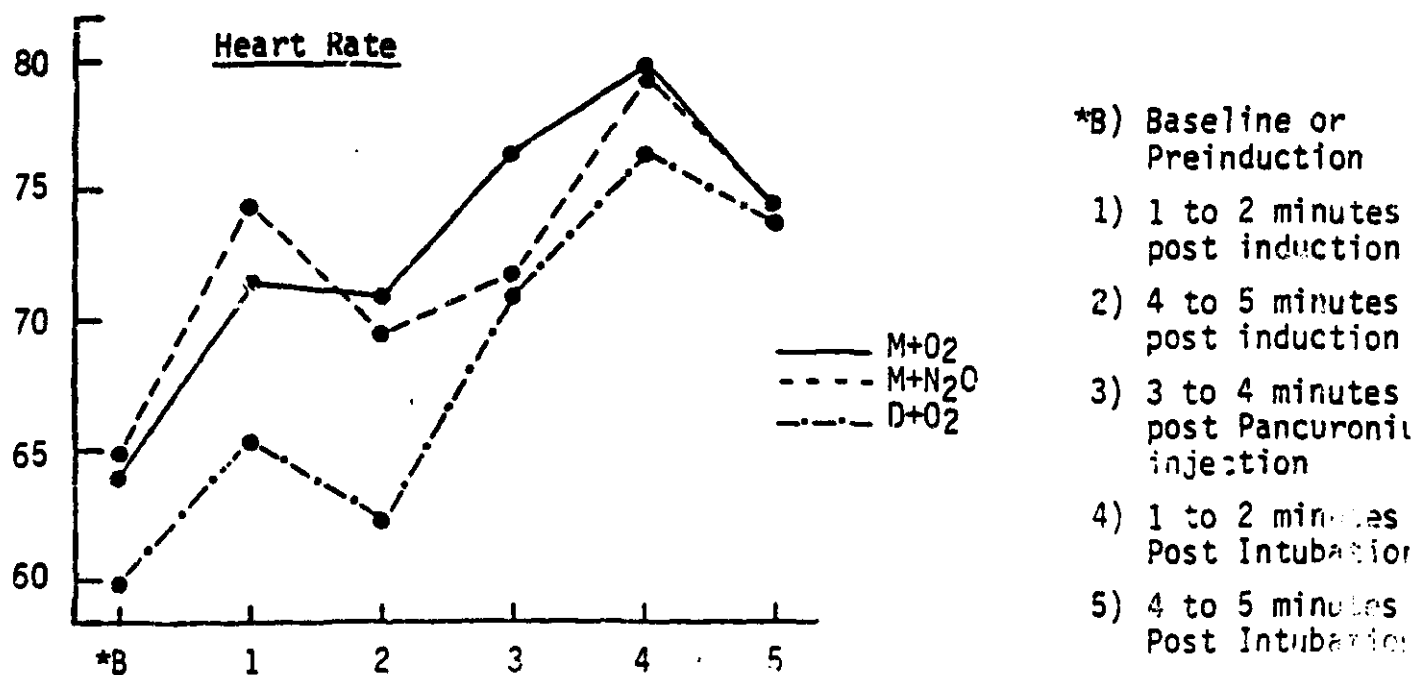
N-18654-6

RESULTSSignificant Deviations from Protocol:

1. The diazepam group was an additional group not specified by the protocol.
2. Systemic vascular resistance was determined in only 18 of the 30 patients. During cardiopulmonary bypass, eight patients received anesthesia induced with midazolam + O₂, three patients with midazolam + N₂O and seven patients with diazepam + O₂.
3. All patients in the midazolam + N₂O group were treated prior to patients in the other two treatment groups, and, therefore, were not assigned to this group randomly as specified in the protocol.

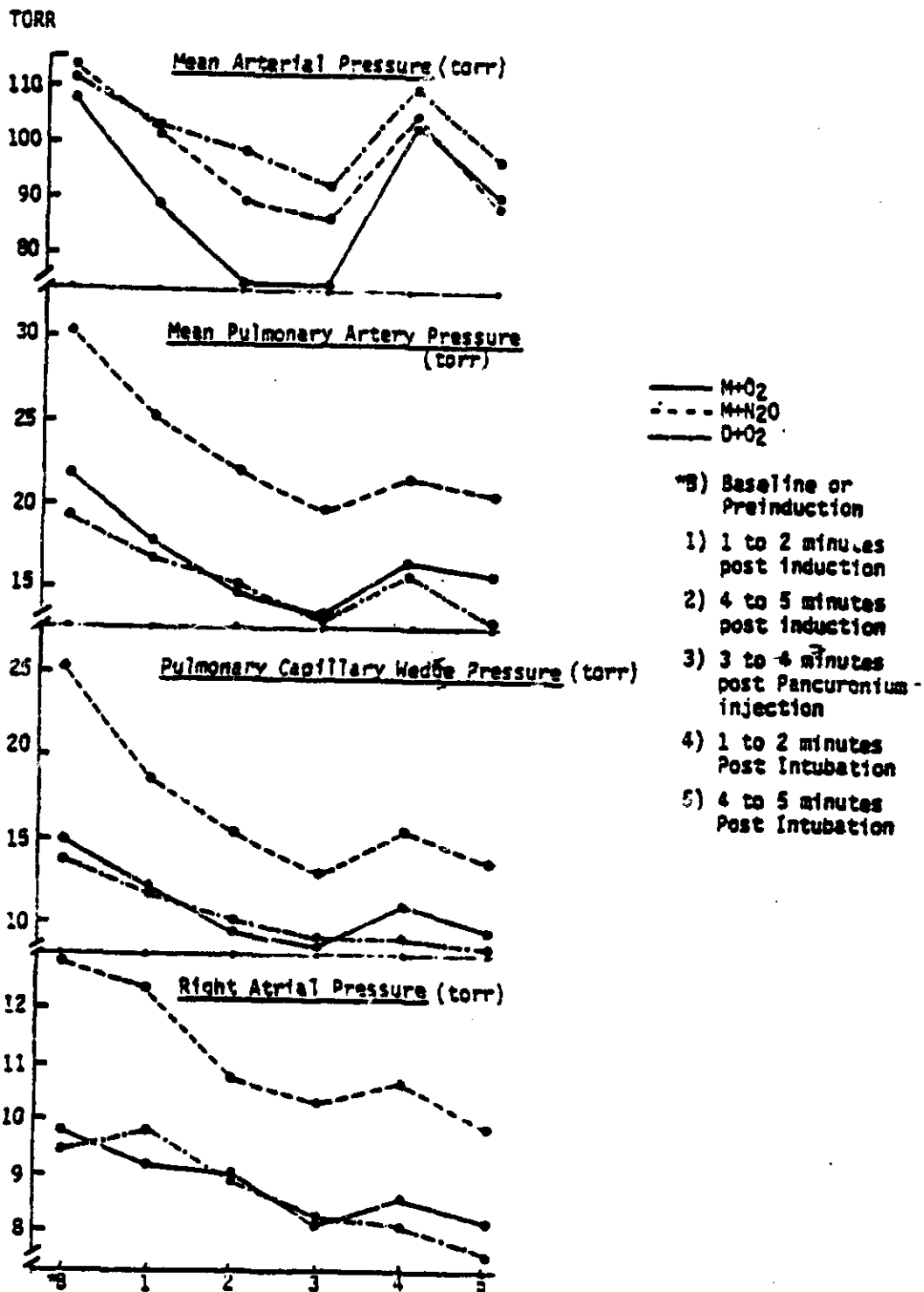
Efficacy:Hemodynamic Parameters:

1. Heart rate: A significantly higher heart rate at four to five minutes post test drug injection was seen with midazolam + O₂ than with diazepam (p=0.03). Even though the mean values for heart rate at four to five minutes post intubation for all groups are similar, the analysis of covariance on the change of pulse rate from three to four minutes post pancuronium demonstrates a significant increase in heart rate for patients receiving diazepam + O₂ as compared with patients receiving midazolam + O₂ (p=0.02) or for patients receiving midazolam + N₂O as compared with those receiving midazolam + O₂ (p=0.02). The mean values for heart rate are shown in Table II and presented graphically in Figure 1.

FIGURE 1

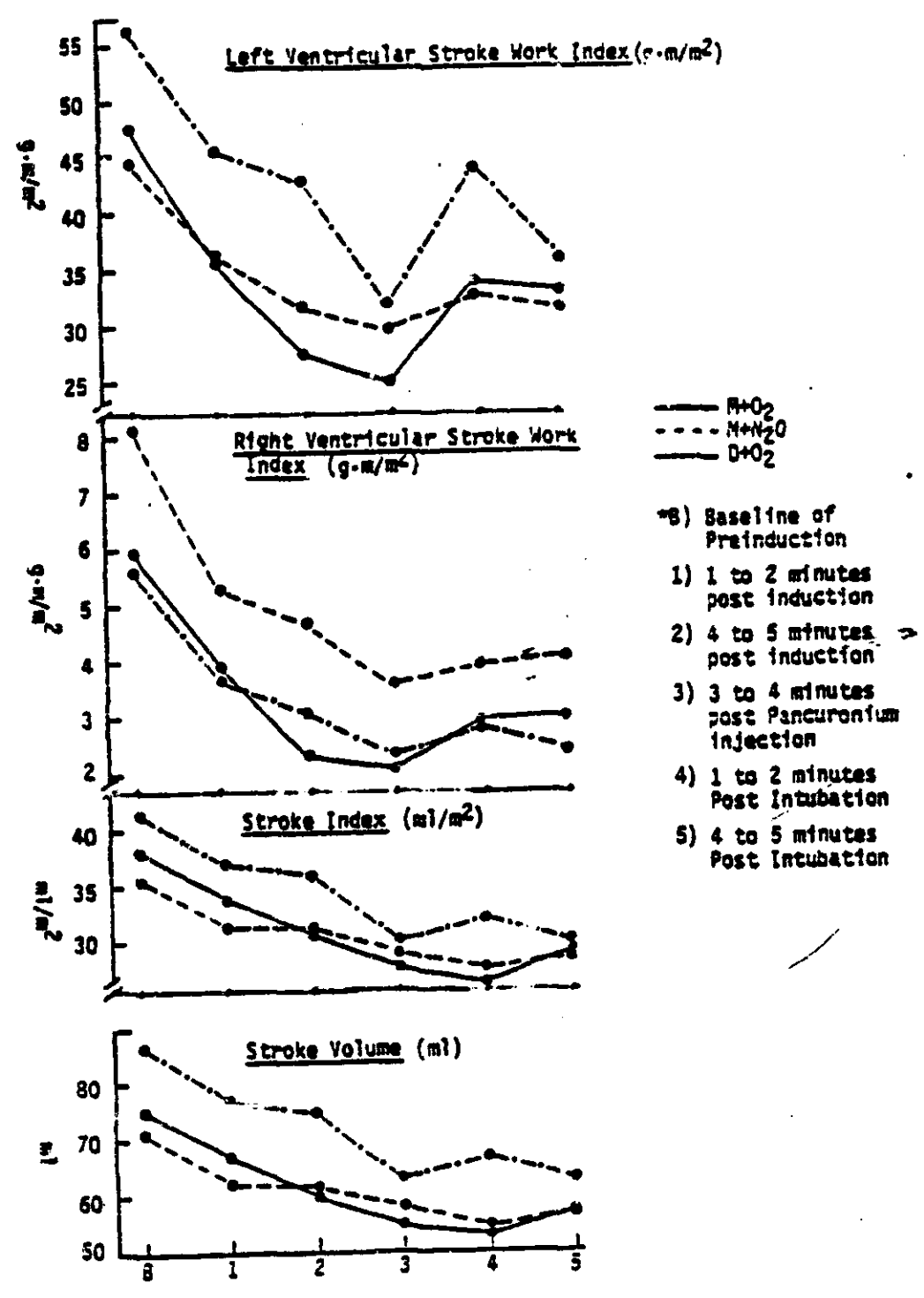
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FIGURE 2



15

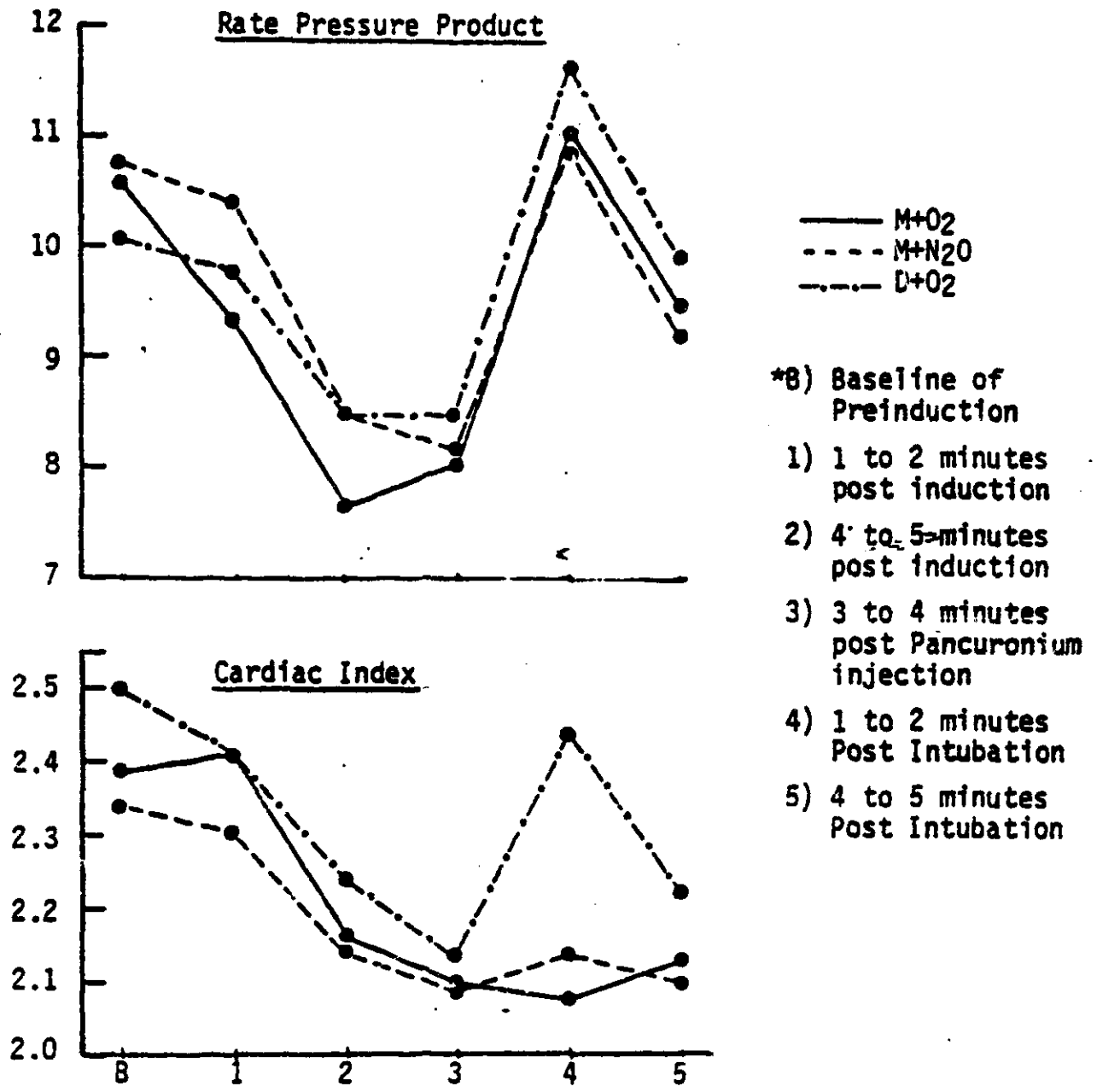
FIGURE 3



74
~~13~~

45

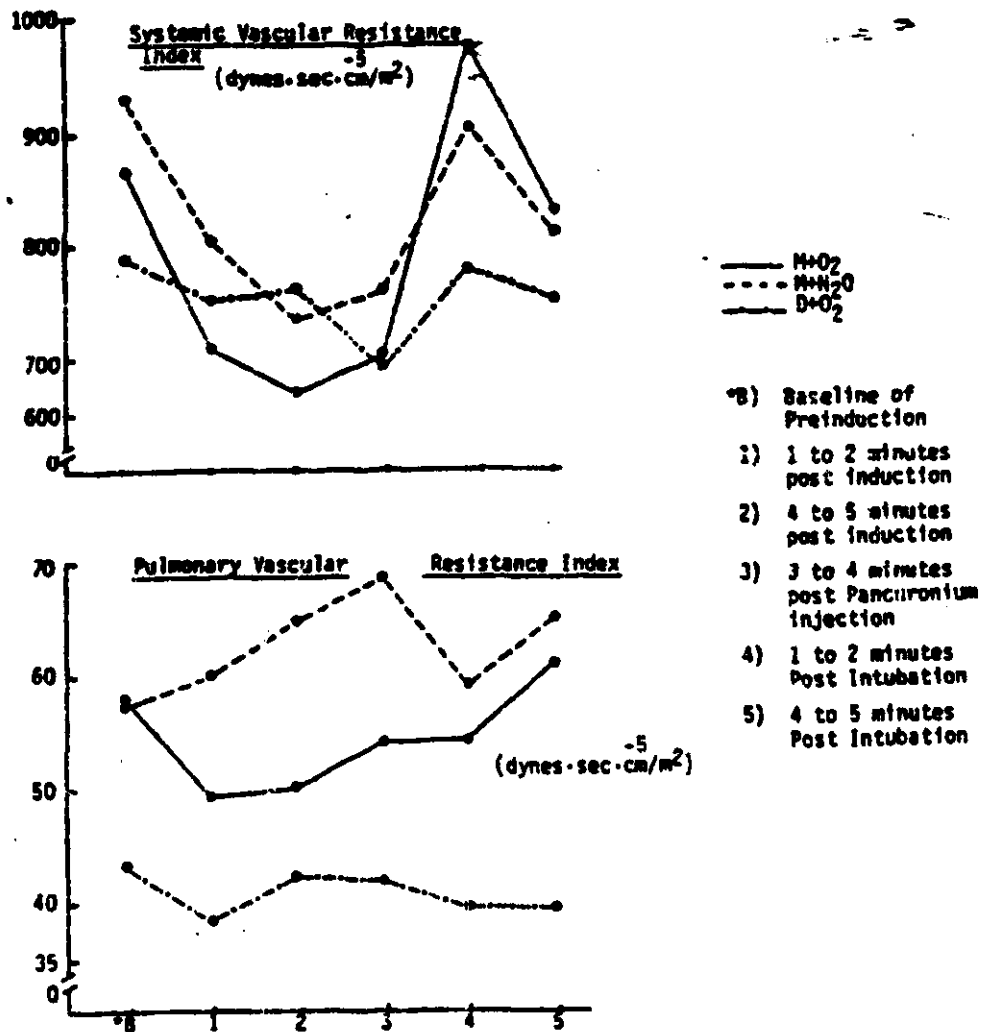
FIGURE 4



4. Resistance Indices:

- a. Systemic Vascular Resistance Index (SVRI). A significantly lower SVRI was seen with midazolam + O₂ than diazepam at four to five minutes post injection (p=0.05). SVRI was increased for all treatment groups at one to two minutes and four to five minutes post intubation from three to four minutes post pancuronium injection. The actual increase was significant with midazolam + O₂ vs midazolam + N₂O (p<0.03) for both post intubation intervals. This increase was also significant for midazolam + O₂ vs diazepam (p<0.01) at one to two minutes post intubation (Figure 5).
- b. Pulmonary Vascular Resistance Index (PVRI). A significantly higher PVRI was seen with midazolam + N₂O vs diazepam + O₂ at four to five minutes post injection (p=0.02), and this value was also significant when compared with that of midazolam + O₂ (p=0.04). Subsequent changes for post intubation intervals were not significantly different between treatments (Figure 5) and Table III (page 11) reports the mean values for these parameters.

FIGURE 5



5. Systemic Vascular Resistance (SVR). During cardiopulmonary bypass, two minutes post test drug injection, a significantly lower SVR was seen for patients receiving diazepam + O₂ than midazolam + O₂ (p=0.01) or midazolam + N₂O (p=0.02) (Figure 6). Table IV reports the mean values for this parameter.

FIGURE - 6

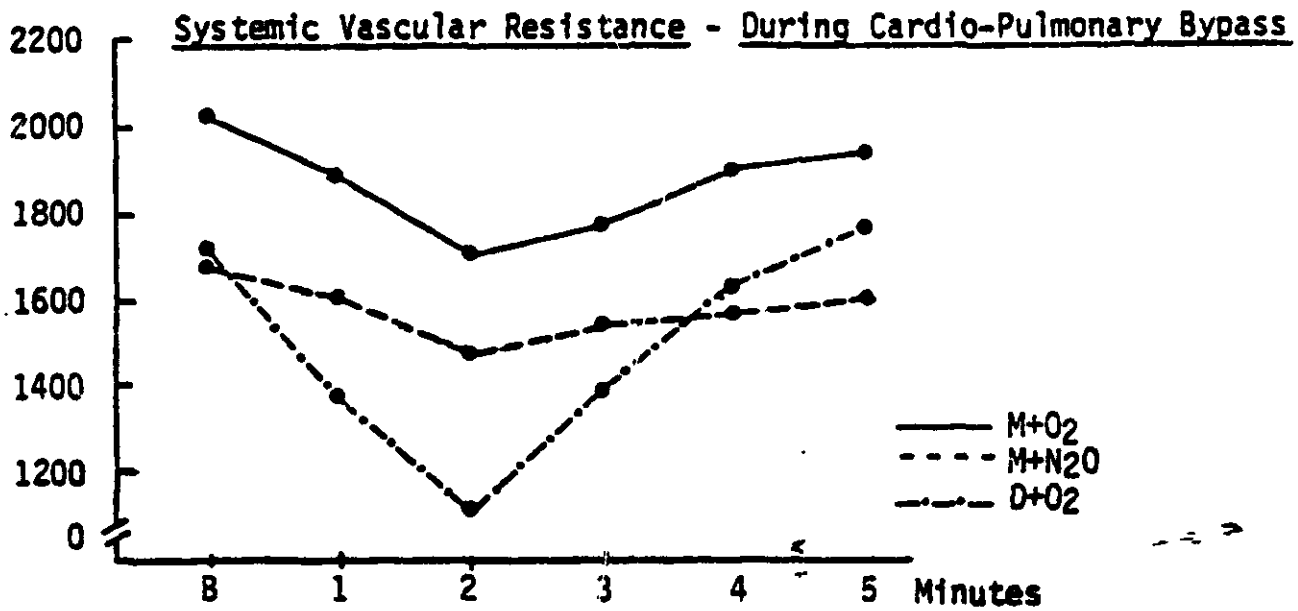


TABLE - IV

SYSTEMIC VASCULAR RESISTANCE DURING CARDIOPULMONARY BYPASS

Test Drug	Baseline	1 minute post drug	2 minutes post drug	3 minutes post drug	4 minutes post drug	5 minutes post drug
M+O ₂	2035.38	1894.13	1700.38	1779.00	1901.86	1943.71
M+N ₂ O	1681.33	1609.67	1479.00	1544.50	1566.00	1606.50
D+O ₂	1724.71	1379.71	1115.71	1394.00	1626.29	1766.29

M+O₂ = Midazolam + O₂; M+N₂O = Midazolam + N₂O; D+O₂ = Diazepam + O₂

SUMMARY OF PROTOCOL 2286 (single institution study)

Robert J. Fragen, M.D., Northwestern. Dr. Fragen's investigational team is well known to and held in highest regard by this reviewer.

A thorough summary of this research project occupies pages 10-17 of the 24 August 1982 summary for _____ therefore, a brief summary should suffice at present. Some loose ends have now been clarified and these will be cited. also

A total of 180 adult surgical patients, 18-61 years of age, about 75% female, evenly matched for each of seven test groups, were divided in double-blind randomized fashion as follows:

midazolam 0.08 mg/kg IM plus scopolamine 0.4 mg IM--25
 midazolam 0.08 mg/kg IM plus atropine 0.4 mg IM--24
 midazolam 0.08 mg/kg IM plus placebo to resemble the anticholinergic injection--27

hydroxyzine 1.5 mg/kg IM plus scopolamine 0.4 mg IM--27
 hydroxyzine 1.5 mg/kg IM plus atropine 0.4 mg IM--24
 hydroxyzine 1.5 mg/kg IM plus placebo to resemble antich. inj.--28

placebo (midazolam vehicle--0.2 ml/10 kg plus placebo for anticholinergic (saline 1 ml, both IM--25))

There were no exclusions from analysis and none needed.

Sedation for midazolam was within the desired range of ^{between} 3 & 4 on the rating scale at 30, 60 and 90 minutes after injection regardless of anticholinergic and with placebo anticholinergic (rating scale is discussed in summary for studies 2198 A & 2199A). Sedation peaked at 30 and 60 minutes after IM injection and had lessened slightly at the time of 90 minute evaluation. The addition of atropine did not change sedation to any clinically significant degree. The addition of scopolamine to midazolam produced more sedation than did midazolam without anticholinergic, but results were also generally in the desired range.

All midazolam groups had a better sedation rating than did the placebo group.

These data also support efficacy of hydroxyzine for the production of preoperative sedation. Onset was slower, with peaking at 60 & 90 minutes. Midazolam produced more sedation than did hydroxyzine under almost all test conditions and at all times; the exception was that hydroxyzine plus scopolamine produced equal sedation to midazolam plus scopolamine at 90 minutes only.

The AVATs data suggests that the investigator staff exerted a non-drug calming influence on patients in all test groups. Preoperative apprehension-anxiety improved, regardless of treatment. Midazolam patients were better off at 30 minute testing than were placebo and hydroxyzine patients, regardless of anticholinergic usage, but there were no differences between groups worth noting at 60 & 90 minute evaluation. Definitive evaluation of the anti-anxiety and/or anti-apprehension effect is being conducted by the Staff of HFN-180.

Pain on injection and later development of reaction at the injection site was limited for all practical purposes to the hydroxyzine patients (58.2% for hydroxyzine and only one case or 1.3% for midazolam).

Dysphoria was reported in 3/25 patients who received the combination of midazolam and scopolamine (12%). In the case of _____ this observation was judged moderate and present for only 20 minutes during emergence from anesthesia. In the case of _____

there is more information: 1. 48 y. f. with cervical carcinoma, 2. Flurazepam 30 mg for sleep the night before, 3. At 30 minutes after injection, the pt. was unable to respond to verbal command and could not perform a 30 minute AVAT test (other AVATS testing times were completed), 4. At 60 & 90 minutes the patient was thrashing around and stumbling incoherently; had slurred speech. 5. She vaguely remembers going to the operating room, 6. No dysphoria was noted after surgery; all of this was limited to the preoperative evaluation period, 7. It was hard to obtain patient cooperation during the time period of this adverse experience, 8. Still, this adverse experience was rated only moderate in severity. The third case involves patient

(23 f for breast biop: y). Dysphoria developed in the recovery room and was judged responsive to physostigmine treatment; since anesthesia is not detailed and since other information, such as dosage of physostigmine, is not provided, no conclusions can be made about this case; anyway, patient management problems appear minimal and severity was rated moderate.

Impairment of recall could not be fully evaluated from the IND summary. This is now clear; see R.J.Fragen, et. al., Can. Anaesth. Soc. J., 30 (#2): 136-141, 1983 and see new summary.

To test retrograde amnesia, a ballpoint pen was shown before injection. To test anterograde amnesia, three memory cards were shown (picture of a dollar bill, picture of a shoe and picture of a bird) 30, 60 and 90 minutes after injection; the selection of a particular memory card (only one was shown for each time interval) was by random sequence ~~which varied from patient to patient.~~ The next day, patients were asked to recall the pictures. If they could not, a composite of six pictures, including the three previously shown, was presented and they were asked to identify the pictures previously shown. Drug induced anterograde amnesia was considered to exist only when there was a failure to both recall and recognize the memory picture.

and each patient eventually saw all three cards

~~reference to 22 patients who had received~~

Seven percent of the patients who received midazolam did not recall the ballpoint pen. They did, however, recall other immediate pre-injection events and were not considered to have retrograde amnesia. All other patients recalled the pen.

When all patients who received midazolam are considered, 50% manifested amnesia for the memory card picture shown 30 minutes after injection; 36.1% for the memory card picture shown 60 minutes after injection. Atropine did not significantly alter the impairment of recall noted after the injection of midazolam. Scopolamine enhanced and/or prolonged the impairment of recall noted after injection of midazolam; fifty percent of the patients tested 90 minutes after injection of the midazolam-scopolamine combination could not recall the memory card picture shown at that time (10/20). Midazolam was generally superior to placebo and hydroxyzine groups, as is obvious from the table reproduced ~~below (from page 140 of the Fragen reference cited above)~~ at the top of the next page (from page 140 of the Fragen reference cited above):

manifested amnesia

or recognize

TABLE III Failure to both recall and recognize memory pictures

Drug(s)	Time after injection (min)		
	30	60	90
Midazolam	10/26*	6/26‡	3/19
Midazolam + atropine	14/22*	10/22*	3/15
Midazolam + hyoscine	12/24*	10/24*	10/20†
Hydroxyzine	0/26	2/26	1/19
Hydroxyzine + atropine	1/23	1/23	0/16
Hydroxyzine + hyoscine	1/27	2/27	4/23
Placebo	0/22	0/22	0/13

Number of patients who both failed to recall and recognize memory pictures/number of patients in the group at each time interval.

*p < 0.05 versus all hydroxyzine groups and placebo.

†p < 0.05 versus hydroxyzine, hydroxyzine + atropine and placebo.

‡p < 0.05 versus placebo.

Eight patients were rated as asleep with no response to verbal commands in a normal tone of voice, usually for only one test period but sometimes two. Three received midazolam alone, 3 received midazolam and atropine and 2 received midazolam and scopolamine. The time period of 30 minutes post-injection predominated, with five such cases at that time. This observation, in this study, generally interfered with the Treiger Test for that time period and with the showing of the Memory Card for that time period. Beyond that, seven of the eight cases posed no patient management problems. The exception was patient already discussed.

REVIEWER'S IMPRESSION:

These data support efficacy of 0.08 mg/kg IM midazolam for premedication, with and without intercurrent use of anticholinergics. The peak is from 30-60 minutes after injection. Hydroxyzine 1.5 mg/kg IM was also effective, though somewhat less than midazolam, peaking later at 60-90 minutes after injection.

Midazolam patients felt that they had more relief of anxiety at 30 minutes after injection, compared to other groups. At other test times there was no significant group difference. Definitive review of this claim is being conducted by the staff of HFN-160.

Hydroxyzine commonly produced pain at the injection site. Midazolam did not.

The combination of midazolam and scopolamine produced dysphoria in 12% of the cases (3/25).

Midazolam produced approximately 50% impairment of recall, with testing reinforced. This observation peaked at 30 minutes after injection. Scopolamine enhanced and prolonged impairment of recall. Because of the reinforcement used in testing, this reviewer feels that the impairment of recall seen under ordinary clinical conditions should be even greater.

Study 2202

Walter L. Way, M.D. & Paul F. White, M.D., Anesthesia, Univ. of Calif.,
San Francisco (Dr. Way is Prof. of Anes., Dr. White is now at Stanford Univ.).

This was a study in 80 ASA Risk I & II patients requiring emergency surgery (thus classified ASA IE & IIE), of which 69 were suitable for analysis. Patients were considered to have full stomachs or at least have some danger of aspiration because of the emergency nature of surgery, thus the trachea was intubated as rapidly as reasonably possible around the time of induction ~~with a~~ ~~laryngeal mask~~ (cuffed endotracheal tube, inflated at the time of intubation). In some of the cases (13) it was clinically feasible to empty some stomach contents by nasogastric tube prior to induction. Patients were selected who could respond to questions posed. Premedication was with glycopyrrolate 0.005 mg/kg intravenously around the time of induction. Exclusions from analysis were because nine patients had received narcotics or alcohol (presumably before admission in the case of alcohol but the summary is not specific on this point) prior to the procedure.

First: Three to 6 mg of d-tubocurarine was administered, as is traditional at UCSF for such cases, to attenuate the fasciculations anticipated later from administration of succinylcholine. Second: Patients were divided into four groups to receive the following for induction of anesthesia 1. midazolam 300 ug/kg (n = 20, 1 exclusion), 2. ketamine 1.5 mg/kg (n = 20, 2 exclusions), 3. a combination of midazolam 150 ug/kg and ketamine 750 ug/kg (n = 20, 2 exclusions), & 4. thiopental 4 mg/kg (n = 20, 4 exclusions); in actual practice, the first few patients received slightly higher doses and then the dose was reduced based on that experience. The study drug was given as a bolus. Third: Immediately after administration of the test drug, succinylcholine 1.5 mg/kg was administered intravenously. This was followed as quickly as possible with catheterization (intubation) of the trachea. Patients were administered 100% oxygen, starting with the administration of d-tubocurarine; the test drug was given after 3 minutes of oxygenation. Patient assignment was by randomized code; the anesthesiologist monitoring the patient during anesthesia, recovery and postoperatively was not aware of the test drug administered. Anesthesia was maintained with nitrous oxide in oxygen. Muscle relaxation for surgery was provided with an initial dose of 200 ug/kg d-tubocurarine, followed by 3 mg increments as needed to maintain relaxation. Morphine 1-3 mg was administered as needed for signs of lightening of anesthesia. All of this is typically "balanced anesthesia" (supplementation of subpotent nitrous oxide with parenteral central nervous system depressants and/or analgesics & muscle relaxants).

The pharynx was inspected for stomach contents after intubation; none was noted in any of the cases. Presence of vomiting, retching & regurgitation ~~was~~ perioperatively were noted; as part of the followup, signs of aspiration were looked for during the procedure and in the recovery room (none found).

Impairment of recall was tested: Memory card was shown prior to surgery (before induction). When fit for discharge from the recovery room, they were shown pictures of 10 common objects. At 24 hour postanesthetic visit, they were shown 20 pictures, including the memory card (big \$1.00 bill, which seems to have a lasting impression partially because of the enlarged size---it made a lasting impression on me the first time that a drug company showed it during a meeting) and the 10 pictures shown in the recovery room. Retrograde amnesia was judged present if they could not remember the memory card (no retrograde amnesia noted). Anterograde amnesia was considered total if no pictures were recalled, partial if 1-4 were recalled and absent if 5-10 were recalled.

The patients were questioned about dreams in the recovery room, prior to discharge, and again five to seven days later. A Psychologist-Observer recorded the patient's behavior in the recovery room.

RESULTS:

Patient population was typical for an emergency surgical schedule, with a great variety of diagnoses, seemingly well matched per group. Mean age was close to 30 years in all groups (range 18-64); most patients were ASA Status IE (58/80) and the rest were ASA Status IIE. Mean surgical duration was longest in the thiopental group (100 min.) and shortest in the midazolam group (69 min.). The time from test drug administration until inflation of the endotracheal cuff was 2 minutes or less in each group, without much difference between groups. Patients were questioned as to awareness of endotracheal intubation when judged fit for discharge from the recovery room (remember that anesthesia was quite light at the time of intubation); only one patient (thiopental group) remembered the intubation. Patients manifesting purposeful movements during succinylcholine fasciculations were judged "possibly aware" of endotracheal intubation; there were 7 such patients in the midazolam group, 5 in the ketamine group, 5 in the midazolam + metamine group and 2 in the thiopental group.

AMNESIA: As noted, there was no retrograde amnesia. The following table (page 8 of the sponsor's summary in Volume 1.28) is regarding anterograde amnesia:

TABLE V
ANTEROGRADE AMNESIA⁽¹⁾

	Total		Partial		None	
	No.	Pts. %	No.	Pts. %	No.	Pts. %
Midazolam (N=16)	5	31.35	5	31.35	6	37.50
Ketamine (N=17)**	0	0.00	1	5.88	16	94.12
Midazolam + Ketamine (N=15)	2	13.33	3	20.00	10	66.67
Thiopental (N=8)*	0	0.00	1	12.50	7	87.50

*Significantly less amnesia than midazolam ($p < .05$, 2x3 analogue to Fisher's Exact Test)

**Significantly less amnesia than midazolam ($p < .01$, 2x3 analogue to Fisher's Exact Test)

(1) Total = failure to recall all 10 pictures shown previously
 Partial = recall of 1-4 pictures shown previously
 None = recall of 5-10 pictures shown previously

Psychological Observer Notes (when fit for discharge from recovery room): Six patients were judged too drowsy for evaluation (3-midazolam, 1-midazolam + ketamine & 2-thiopental). One midazolam and 1 ketamine patient were judged "not calm"; these two patients and one thiopental patient were judged easily upset. No patients were judged to be violent, hallucinating, hostile or delirious. Thiopental patients were more depressed than midazolam patients & ketamine patients; midazolam + ketamine patients were more depressed than ketamine treated patients. There were no significant differences between groups in the symptoms of agitation, confusion, apprehension, suspicion, irrational behavior, restlessness, emotional instability and resentment.

Dreaming: Patients were questioned in the recovery room or soon afterwards, and again 5-7 days later, about their perioperative dreams. Significantly more ketamine patients had postoperative recall of a dream-like experience during or after operation; at one week evaluation, the ketamine patients continued to have significantly more recall of dreams. Three of the 8 ketamine patients who reported dreams also reported that their dreams were unpleasant. No patients reported recurring dreams. This can be seen from Table VI, below (page 10 of summary in Volume 1.28):

TABLE VI
DREAMING

	Patients Responding Affirmatively							
	MIDAZOLAM (N=19)		KETAMINE (N=18)		MIDAZOLAM + KETAMINE (N=18)		THIOPENTAL (N=16)	
	N	%	N	%	N	%	N	%
Recall of Dreamlike Experience								
Postoperative	0	0.00	8*	44.44	1	5.55	2	12.50
One week later	0	0.00	7**	38.39	2	12.50	0	0.00
Difficulty Separating the Dream World from Reality								
Postoperative	2	11.11	5	27.78	3	16.67	3	18.75
One week later	0	0.00	1	5.56	0	0.00	0	0.00
Afraid Following Operation								
None	18	94.74	13*	72.22	15	83.33	11	68.75
Slight	1	5.26	3	16.67	2	11.11	3	18.75
Very	0	0.00	2	11.11	1	5.56	2	12.50
Worried Following Operation								
None	19	100.00	14	77.77	17	94.44	14	87.50
Slight	0	0.00	3	16.67	1	5.56	1	6.25
Very	0	0.00	1	5.56	0	0.00	1	6.25

*Significantly greater than midazolam ($p < .01$) or midazolam + ketamine ($p < .05$)

**Significantly greater than midazolam or thiopental ($p < .01$)

+Significantly smaller than midazolam ($p < .05$)

Patient evaluation: The results of questions put to patients when they awoke from surgery can be seen from Table VII (same source, page 11). The results of questions put to patients one week later can be seen from Table VIII (same source, same page). These tables are reproduced on the next page. More patients in the thiopental group (81%) stated that they felt depressed than did patients in the midazolam group (5%), ketamine (0%), midazolam + ketamine (17%). Only one patient would object, if necessary, to having the same anesthesia again; this was a ketamine treated patient who testified to experiencing unpleasant dreams.

TABLE VII
PATIENT'S POSTOPERATIVE CONDITION

	MIDAZOLAM (N=19)		KETAMINE (N=18)		MIDAZOLAM + KETAMINE (N=18)		THIOPENTAL (N=16)	
	N	%	N	%	N	%	N	%
Postoperative Status *								
Depressed	1	5.26	0	0.00	3	16.67	13*	81.25
Normal	16	84.21	14	82.35	13	72.22	3	18.75
Great	2	10.53	3	17.65	2	11.11	0	0.00
Presence of Postoperative								
Pain	12	63.16	12	66.67	11	61.11	15**	93.75
Headache	2	10.53	3	16.67	2	11.11	0	0.00
Lightheadedness	2	10.53	2	11.11	2	11.11	3	18.75
Sensation of Room Spinning	0	0.00	2	11.11	0	0.00	3	18.75
Bother following Operation								
Yes - Pain	8	42.11	13	72.22	11	61.11	11	68.75
No	11	57.89	5	27.78	7	38.89	5	31.25

*Significantly greater than all other treatments (p<.01)
 **Significantly greater than midazolam or midazolam + ketamine (p<.05)
 +One patient in the ketamine group reported feeling "drugged,
 difficulty focusing".

TABLE VIII
PATIENT'S FUTURE PREFERENCE

	MIDAZOLAM (N=19)		KETAMINE (N=18)		MIDAZOLAM + KETAMINE (N=18)		THIOPENTAL (N=16)	
	N	%	N	%	N	%	N	%
Would Patient Have Same Anesthesia Again								
Yes	19	100.00	16+	94.12	18	100.00	16	100.00
No	0	0.00	1	5.88	0	0.00	0	0.00
Would Patient Worry In Future								
More worried	0	0.00	2	11.11	0	0.00	0	0.00
Same	1	5.26	5	27.78	7	38.89	11	68.75
Not at all	18*	94.74	11	61.11	11	61.11	5	31.25

*Significantly more than ketamine or midazolam + ketamine (p<.05) or thiopental (p<.01)

+One patient responded "don't know"

Study 2202, page 5ive-----

SAFETY:

As noted before, there was no clinical evidence of aspiration, a dreaded complication of emergency anesthesia. One patient retched on emergence, obviously self limiting.

Anesthesia was judged unusually light in 5 midazolam cases and 1 midazolam plus ketamine cases (around the time of induction and intubation). Not surprising.

One midazolam patient developed mild induration on the second postoperative day at the infusion site. All injectables were administered at this site. Two midazolam plus ketamine patients had mild tenderness at the infusion site several days after surgery. The first of these cases was judged possibly related to test drug administration ~~as was the last case~~ as was the last case. The middle case was judged remotely related to test drug administration. I think that enough drugs were administered at the infusion site in each case to preclude any reasonable association with test drug administration. Note especially that the third case involves a patient who was receiving antibiotics, who already had redness at the time of surgery and who refused to allow the investigator to start another infusion.

Three midazolam patients, 7 ketamine patients, 2 midazolam + ketamine patients and 2 thiopental patients manifested severe increase in mean arterial blood pressure (greater than 50% or required treatment) around the time of induction. I checked five of ~~these cases from~~ the case reports and determined that these episodes were temporally related to endotracheal intubation, not surprising under light general anesthesia. Blood pressure elevation is also in keeping with the clinical pharmacology of ketamine. Some of these cases were really less than 50% change and the rating always involves the addition of enflurane to anesthetic management (deepen anesthesia and thus lower blood pressure); thus these cases were classified severe on the basis of sometimes adding treatment and that treatment was enflurane.

Five patients in the midazolam + ketamine group and one patient in each of the other groups manifested severe increase in heart rate around the time of induction. A spot check of case records reveals a temporal relationship to intubation. Management, in the cases checked, was by enflurane, as above. addition of

Immediately post induction, the mean increase in mean arterial pressure was: 1. midazolam 36 mmHg, 2. ketamine 30, 3. mid. & ket. 26, 4. thiopental 32. Pulse rate increase at this time (mean) was: 1. mid. 25, 2. ket. 32, 3. mid. & ket. 16, 4. thio. 20. There seems to be no mean increase in keeping with the clinical pharmacology of ketamine alone but note that "severe" increases were more common in patients who received ketamine; "severe" increase seemed to be any case where enflurane was added to treatment.

Hematological, biochemical and urinalysis screening was performed, with most tests being performed in the majority of patients, before and 5-7 days after surgery. There was a scattering of deviations from normal but no severe changes in biochemical screening; changes were about equal between test groups and all changes were judged by the investigator to be remotely related to test drug administration (remotely being the lowest rating possible). The summary tables note the presence and absence of deviations from normal limits but do not provide individual figures, as is common practice in this application.

Study 2202, page six-----

REVIEWER'S CONCLUSIONS AND/OR COMMENTS:

Midazolam appears suitable as part of the overall management of emergency "crash" intubation (full stomach precautions or danger of aspiration greater than usual precautions). These patients are, obviously, very light. One patient in the midazolam group even remembered the trachea being catheterized, but this appears to be no big deal. Pulse and, especially, mean arterial pressure (calculated from systolic and diastolic pressures) rose shortly after induction; this is an expected observation in view of the precautions taken to guard against aspiration and does not appear reasonably associated with the administration of midazolam as such. The investigator's management of the cases judged to represent severe vital sign changes was traditional, deepen anesthesia (in these cases by addition of enflurane). The sponsor's summary seems to have missed this; I dug it out from sampling of the case reports. No unusual postoperative psychological manifestations were revealed. Ketamine was associated with more recall of dreams, sometimes unpleasant; there were no recurrences. Thiopental patients were generally more depressed immediately postoperatively; I don't know what this means.

Midazolam appears associated with what is best described as "impairment of recall". The sponsor prefers the term "amnesia", but this does not seem correct based on my evaluation. Still, there is some precedent to consider. The sponsor cites a letter regarding diazepam, another benzodiazepine, which asked that "amnesia" be listed as an adverse reaction. The term "impairment of recall" precisely describes the less than 100% and often less than complete impairment of recall that I have seen repeatedly; ~~but~~ some compromise may be indicated in consideration of the letter in question.

PROTOCOL 2201A---DOSE RANGING---Single Institution Study --Intramuscular Injection

Robert J. Fragen, M.D., Northwestern

Ten healthy volunteers, age ranging from 23-46 years, male, underwent double-blind dose range testing; one placebo was randomly assigned during ascending dose sequence. It was agreed in advance that the testing would be halted once the desired dosage and response was obtained, thus only 4 subjects received placebo. Sedation was evaluated serially over eight hours. Subjects were practiced in the Treiger Test, a standard test of ability to connect dots on a sheet of paper. This test was given prior to test drug administration and at 1, 2 & 6 hours afterwards. Serial plasma samples were obtained from 5 subjects in conjunction with 0.05 and 0.075 mg/kg dosage of midazolam and for 24 hours afterwards. Pharmacokinetic information was calculated, using plasma level data, etc.

Sedation was judged inadequate in 9/10 subjects after the administration of 0.05 mg/kg midazolam IM. The exception concerns the oldest volunteer, aged 46 years; he was quite sleepy and drowsy, but never missed a Treiger Test; at a later interview he offered the information that he was "walking on air" for about 12 hours; this was considered a good premedication effect but of such magnitude that it was deemed un-necessary to test the next dose, 0.075 mg/kg, in this subject.

The dose of 0.075 mg/kg was judged to produce satisfactory sedation in 8 of 9 subjects so tested. It was decided that this dose was sufficient, therefore, only one subject received 0.1 mg/kg IM. Without the apprehension that usually is associated with patients awaiting surgery, these volunteers generally manifested more profound effect than that seen in surgical patients. Five of nine subjects were unresponsive to verbal commands or questions in a normal tone of voice at 45 minutes after test drug administration and there was a scattering of such results at other times (30 to 120 minutes after injection). Most of the time, these subjects could be awakened sufficiently, with more effort, to complete the Treiger Test; thus, most serial Treiger Tests were completed despite the sedation rating of 1 (1 = asleep/no response to verbal command in normal tone of voice---as for the clinical studies).

Serial Treiger Tests showed only minimal impairment of psychomotor abilities following administration of 0.05 and 0.075 mg/kg midazolam IM. Following the administration of the 0.075 mg/kg dose, subjects missed 23.9% and 18.1% of the dots at one and two hour tests, respectively. Total mm deviation for dots missed was small, usually about 1 mm. Six hour testing following injection of 0.075 mg/kg midazolam was comparable to baseline testing. Placebo treatment had no appreciable effect on Treiger Test performance. At the higher dose (0.1 mg/kg), the one subject so tested manifested greater impairment of Treiger testing than had been seen in this subject for lower doses, however, performance was again comparable to baseline at the time of 6 hour testing.

Two of four subjects were slightly drowsy after placebo injection and another eventually lost interest in reading to kill the time away. These people were judged not to be at their mental peak for the day so early in the morning, and this was judged to be qualitatively different from the usual midazolam drug effect. Two placebo subjects also reported slight headaches which went away soon after testing was completed for the day.

Pharmacokinetics:

Mean terminal half-life ($t_{1/2}$ beta): 0.05 mg/kg = 2.6 hrs. (range 2-3.4 hrs.)
0.075 mg/kg = 2.1 hrs. (range 1.7-2.6 hrs.)

Clearance: 0.05 mg/kg = 0.45 l/hr/kg
0.075 mg/kg = 0.44 l/hr/kg

Volume of Distribution: 0.05 mg/kg = 1.71 l/kg (range 1.61-1.83)
0.075 mg/kg = 1.36 l/kg (range 0.83-1.92)

Protein binding: One hour after plasma sample, the protein binding was a mean of 97.0% for the 0.075 mg/kg dose (range 95.9-97.6%).

Maximum plasma concentration: 31 ng/ml (range 25-35) for the 0.05 mg/kg dose, at a mean of 0.43 hours after injection.
68 ng/ml (range 42-103 ng/ml) at a mean of 0.23 hours after injection for the 0.075 mg/kg dose.

SAFETY:

There were no clinically significant changes in mean arterial pressure during the testing period of 8 hours. Heart rate increased 4-8 hours after administration of the 0.075 mg IM dose of midazolam, but not after 0.05 mg/kg. The increase was from a mean value of 66.4/minute at baseline to a peak of 78.2 at 6 hours (74.2 at 4 hours, 76.9 at 8 hours, after essentially no change 1 hour after injection). There were no changes in respiration (evaluated mainly as respiratory rate). Three subjects reported headaches the afternoon and evening following administration of 0.075 mg/kg, and also two during placebo testing which resolved quickly after testing was completed for the day.

Erythema at the injection site was noted 24 hours after injection in one subject who received 0.075 mg/kg and the one subject who received 0.1 mg/kg.

Laboratory abnormalities were essentially limited to elevated creatinine phosphokinase, in the range of 40-379 for the dose of 0.75 mg/kg, for instance; pre-study CPK was also elevated in the range of 50-545 mu./ml (normal range for Northwestern is 5 to 25 mu./ml). The volunteers were athletic in nature (runners, weight lifters &/or swimmers) and this was thought to account for the elevated values. The highest mean CPK noted following injection of placebo was 229.3 mu/ml, and this was the highest mean value reported.

SUMMARY:

The dose of 0.075 mg/kg was established, in this study, to produce the desired degree of sedation with no unusual side effects. Keep in mind that volunteers do not have the preoperative apprehension that bothers most surgical patients and that drug testing proved somewhat restrictive to this relatively athletic group of volunteers. Note one case of relatively mild prolonged effect (about 12 hours by subject history), following the smaller dose of 0.05 mg/kg. Note some sleepiness produced by placebo, ascribed to the life style of the volunteers.

Summary of Protocol 2198A

Investigators: Alan A. Artru, M.D., Univ. of Washington, Seattle
 M. Saeed Dhamme, M.D., Med. Coll. Wisconsin, Milwaukee
 I. Stride E. Seifen, M.D., Univ. of Arkansas, Little Rock (Studied I & II, Seifen)
 Ballard Wright, M.D., Univ. of Kentucky, Lexington
 Robert L. Watson, M.D., Walter Reed A&C

Method:

This was a double-blind, randomized, multi-institutional comparison of midazolam 0.07 mg/kg IM (5 mg/ml vials) and an equivalent volume of placebo IM for preanesthetic medication. Patients were judged good risk (ASA I & II), ranged in age from 18-68 years (mostly in intended range of 18-60 years, with mean age of 31.6 for midazolam and 34.2 for placebo), ranged in weight from 40-155 kg (mean 72 kg); sex distribution was 23% male and 77% female. The two groups were comparable. In addition, patient groups were broken down by induction agent administered later after premedication evaluation (midazolam, thiopental or ketamine) but no information essential to this application was learned thus. Data gathering was by nurse-monitor.

A total of 125 patients participated in the study and 96 cases were judged suitable for efficacy analysis. One investigator (M.S. Dhamme) initially misunderstood the protocol (14 exclusions), in some cases AVATs data was not completed, one patient had a breast examination the AM before surgery and this was judged disruptive of sedation evaluation, etc. For additional exclusion details see pages 5 & 6 of Volume 1.91 and individual summaries in Volume 1.92.

There were two major areas of efficacy evaluation:

A. SEDATION

Sedation was graded before treatment and at 15, 30, 45 and 60 minutes following IM injection, while patients were awaiting surgery. Rating was according to the following scale:

- 6 = hyperactive
- 5 = awake/alert
- 4 = awake/drowsy
- 3 = asleep/easily responds to verbal commands or questions
- 2 = asleep/difficulty in obtaining response to verbal commands
- 1 = asleep/no response to verbal commands

Verbal commands were given in a normal tone of voice and were limited to:

- "(Patient's name), how do you feel?"
- "(Patient's name), where are you?"
- "(Patient's name), what day of the week is it?"

It can be seen that intermediate ratings of 3 & 4 were most desirable. Hyperactive would be the least desirable rating for a premedicant. Asleep with no response to verbal commands in a normal tone of voice would also be undesirable, making allowances for the lightness of the stimulus (in practice, so few patients were rated "1" in any studies at any test time for this dosage, and none for Protocol 2198A, that this was an insignificant problem).

B. ANXIETY VISUAL ANALOG TEST (AVAT)

This evaluation of degree of preoperative anxiety or apprehension and the effect of premedication, serially evaluated, was performed and patients were selected to participate in the study only if they scored greater than 50% on a scale ranging from no anxiety (0%) to maximum (100%).

This aspect of the investigation is under definitive review by the staff of

IFN-120 and will only be cited briefly in this review.

Safety evaluation consisted of ordinary clinical measurements, this not being a special study of safety. Blood pressure and pulse were recorded every 15 minutes from premedication through the end of anesthesia, etc. Of interest here are vital sign fluctuations noted while the patients were awaiting surgery; at this time the patients were awake and considerable fluctuation would seem logical while awaiting surgery.

Mild = change greater than 20% but less than 30%

Moderate = change greater than 30% but less than 50%

Severe = change greater than 50% or any change requiring treatment

Results (tables and graphs ["figures"]) are from the sponsor's summary:

TABLE 2 - DEGREE OF SEDATION				
Observation Time	Mean Sedation Scores* (Δ)			
	N	Midazolam	N	Placebo
Baseline	49	5.2 -	47	5.1 -
15 Minutes	48	4.6 (-0.6)*	47	4.9 (-0.2)
30 Minutes	48	3.9 (-1.2)*	47	4.6 (-0.5)
45 Minutes	46	3.7 (-1.5)*	45	4.5 (-0.6)
60 Minutes	41	3.4 (-1.7)*	36	4.5 (-0.6)

* Probability ≤ 0.05 (Analysis of covariance; one-sided vs. placebo)

+ Sedation Scale: 6=Hyperactive; 5=Awake/Alert; 4=Awake/Drowsy
3=Asleep/Easily responds to verbal commands;
2=Asleep/Difficult response to verbal commands;
1=Asleep/No response to verbal commands.

The following is also worth noting: No patients were rated as "1" at any time. Ratings of 3 & 4 were noted at 45 minute testing in 89% of midazolam patients and 42% of placebo patients. Ratings of 3 & 4 were noted in 80.5% of midazolam patients and 36% of placebo patients at time of 60 minute testing.

Figure 1

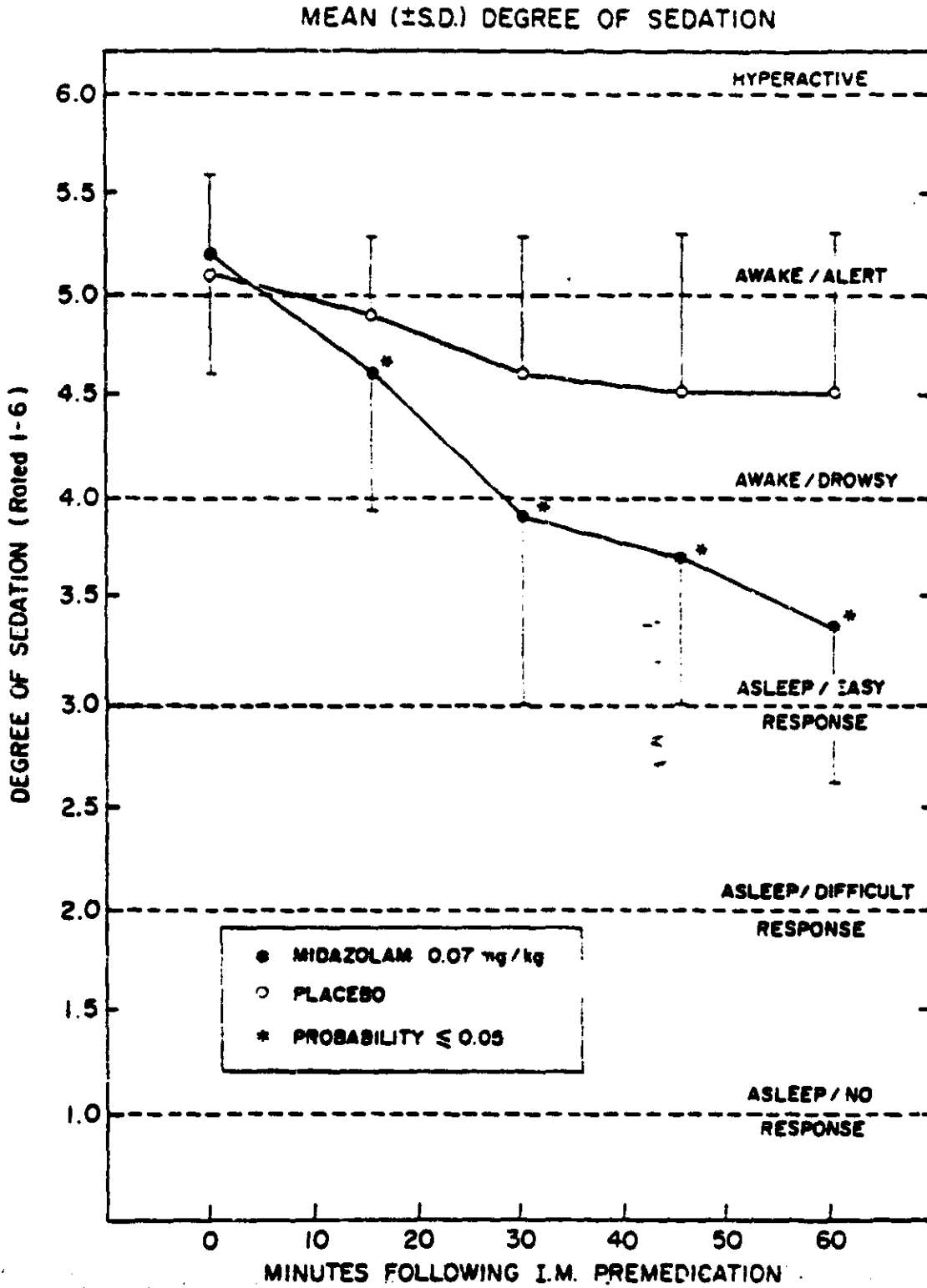


Table 3 illustrates the rapid onset of sedation among patients who received midazolam. Fifteen minutes after administration, 37.5% of the midazolam-treated group (18/48) were either drowsy or asleep. By comparison, 7 of the 47 placebo-treated patients (14.9%) were drowsy and none were asleep.

2198A--page four----

The pooled data revealed no significant difference between midazolam premedicated patients and placebo premedicated patients in serial AVAT testing.

Investigators rated premedication satisfactory in 91.8% of midazolam patients and 48.9% of placebo patients.

SAFETY:

1. Vital signs: This reviewer feels that what can be learned from vital sign observations is limited to the time between injection of test drug and the start of anesthesia; after the start of anesthesia, many other drug and non-drug factors not previously encountered are added to the study. The following vital sign changes were noted during the pre-anesthetic period but after injection of test drug:

	PULSE		PULSE	
	Mild Increase	Mild Decrease	Moderate Increase	Moderate Decrease
Midazolam	3/64 4.7%	5/64 7.8%	0/64 0%	2/64 3%
Placebo	4/61 6.6%	5/61 8.2%	2/61 3.3%	1/61 1.6%
	Mean Arterial Pressure		Mean Arterial Pressure	
	Mild Increase	Mild Decrease	Moderate Increase	Moderate Decrease
Midazolam	1/64 1.6%	6/64 9.3%	0/64 0%	0/64 0%
Placebo	4/61 6.6%	1/61 1.6%	3/61 4.9%	0/61 0%

Mild change (increase or decrease) for this and all studies, unless noted otherwise, is defined as a change from pre-drug administration of greater than 20% but less than 30%. Similarly, moderate change is defined as an increase or decrease in vital sign of more than 30% from baseline (pre-drug administration) but less than 50%. Severe change is defined as a change greater than 50% from baseline or a change that requires treatment. There were no severe vital sign changes noted in this study during the pre-anesthetic period.

The organization of this information in the NDA is somewhat different. The above table was prepared by me with the assistance of Karen K. Church of ROCKE. If necessary, the tables on which the above is based will be submitted to the NDA after a disposition letter has issued; I do not feel that it will be necessary. Note that data from all 125 cases are included in safety evaluation.

No patients manifested both increase and decrease of the same vital sign at different times but one patient manifested mild pulse rate decrease at one time interval and moderate pulse rate decrease at another time interval (this patient received midazolam for premedication).

2. Pain at the injection site: Pain at the injection site was noted in two patients for midazolam and two patients for placebo. In one midazolam patient this was attributed to test drug administration and in the other case it was attributed to postoperative medication. The two placebo patients also manifested erythema, not reported for midazolam.

3. Pre and postoperative hematological and biochemical screening was performed in 22 patients. No abnormalities reasonably associated with test drug administration were uncovered.

INDIVIDUAL HIGHLIGHTS:

Most of the data come from Artru (15 midazolam patients and 15 placebo patients), Dhanre (22 midazolam patients and 21 placebo patients) and Seifen (16 midazolam patients and 15 placebo patients). Seifen (3 midazolam patients and 2 placebo patients), Watson (3 midazolam and 3 placebo patients) and Wright (5 midazolam and 5 placebo patients) contributed less and not enough for analysis of results of induction by agent used (irrelevant to evaluation of premedicant action at any rate).

I
II

Only Artru showed a difference in AVATS evaluation in favor of midazolam. Preoperative anxiety was reduced by 50% between pre-test period and the time that patients were called to surgery in the midazolam group and only 12% in the placebo group. As before, noted definitive evaluation is being conducted by the staff of HFN-160.

In the opinion of this reviewer, other comparative information is non-essential to the evaluation of this potential INDICATION for midazolam.

Reviewer's Impression:

The dose of 0.07 mg/kg IM midazolam was administered for pre-anesthetic medication and data was gathered afterwards for an hour, while patients were awaiting surgery. Onset of action was within 15 minutes. In this study the peak effect was noted at the last testing period, one hour after injection. Sedation was within the desired range, neither too light nor too deep. Side effects were limited for all practical purposes to one, or perhaps two, cases of pain at the injection site, without subsequent development of erythema at that site. Vital sign changes were compatible with normal variation in patients on call to the operating room. Increased mean arterial pressure, mild to moderate, was noted more commonly in patients premedicated with placebo than in patients premedicated with midazolam. Decreased mean arterial pressure was seen more commonly in patients premedicated with midazolam; these changes were again mild to moderate and never required management as an adverse experience. Pulse rate changes greater than 20% were seldom noted, but when noted there was no significant treatment related difference (midazolam versus placebo). Keep in mind that non-drug factors contribute to vital sign changes in patients awaiting surgery.

of
midazolam

Definitive evaluation of AVATS results is being conducted by the staff of HFN-120.

3. Pre and postoperative hematological and biochemical screening was performed in 22 patients. No abnormalities reasonably associated with test drug administration were uncovered.

INDIVIDUAL HIGHLIGHTS:

Most of the data come from Artru (15 midazolam patients and 15 placebo patients), Dhame (22 midazolam patients and 21 placebo patients) and Seifen (16 midazolam patients and 15 placebo patients). Seifen (3 midazolam patients and 2 placebo patients), Watson (3 midazolam and 3 placebo patients) and Wright (5 midazolam and 5 placebo patients) contributed less and not enough for analysis of results of induction by agent used (irrelevant to evaluation of premedicant action at any rate).

Only Artru showed a difference in AVATS evaluation in favor of midazolam. Preoperative anxiety was reduced by 50% between pre-test period and the time that patients were called to surgery in the midazolam group and only 12% in the placebo group. As before, noted definitive evaluation is being conducted by the staff of HFN-160.

In the opinion of this reviewer, other comparative information is non-essential to the evaluation of this potential INDICATION for midazolam.

Reviewer's Impression:

The dose of 0.07 mg/kg IM midazolam was administered for pre-anesthetic medication and data was gathered afterwards for an hour, while patients were awaiting surgery. Onset of action was within 15 minutes. In this study the peak effect was noted at the last testing period, one hour after injection. Sedation was within the desired range, neither too light nor too deep. Side effects were limited for all practical purposes to one, or perhaps two, cases of pain at the injection site, without subsequent development of erythema at that site. Vital sign changes were compatible with normal variation in patients on call to the operating room. Increased mean arterial pressure, mild to moderate, was noted more commonly in patients premedicated with placebo than in patients premedicated with midazolam. Decreased mean arterial pressure was seen more commonly in patients premedicated with midazolam; these changes were again mild to moderate and never required management as an adverse experience. Pulse rate changes greater than 20% were seldom noted, but when noted there was no significant treatment related difference (midazolam versus placebo). Keep in mind that non-drug factors contribute to vital sign changes in patients awaiting surgery.

Definitive evaluation of AVATS results is being conducted by the staff of HFN-120.

SUMMARY OF PROTOCOL 2199A

Investigators: Raymond Miller, M.D., Mt. Sinai M.C., NYC.
 Vera Slavic-Svircev, M.D., Univ. of Wisconsin, Madison
 H. Ronald Vinik, M.D., Univ. of Alabama, Birmingham
 Koloph Hartung ("Buddy") Giesecke, M.D., Univ. of Texas Southwestern
 Med. School, Dallas

Method:

This multi-institutional study was double-blind, randomized and consisted (in all but 4 cases) of ASA Status I & II patients. Three preanesthetic medications were compared:

Midazolam 0.07 mg/kg IM in solution of 5 mg/ml—102 patients with analysis conducted in 101 of the 102 cases.

hydroxyzine 1.0 mg/kg IM in solution of 50 mg/ml—102 patients with analysis of 101/102 cases.

Placebo matched in volume as if it were midazolam solution—106 patients with analysis of 105/106 cases.

TOTAL: 310 total patients with analysis of data in 307 cases.

The patient population was comparable between test groups as to age (32.1 to 34.6 years mean between groups), mean weight (67-71 kg mean between groups) and reasonable spread of primary diagnoses. The protocol called for patients between the ages of 18-60 years and all patients were within this age range. Eighty six percent of the patients were female and 14% of the patients were male. Patients were enrolled if their AVAT evaluation the night before surgery was greater than 50% and if they were otherwise within entry criteria.

Three of Dr. Vinik's patients were excluded for various protocol violations. All other cases were evaluated for preoperative sedation, the most essential part of the study. Six patients had surgery cancelled after premedication so data on these patients was limited to the preanesthetic period. There were fewer sedation observations towards the end of the evaluation period because some patients were called to the operating room earlier than expected. Some patients manifested no anxiety or an AVAT of zero on the morning of surgery; they had qualified for the study by an AVAT greater than 50 (50 mm on a scale up to 100 mm or 50%) the night before surgery and thus were entered in the study; the AVAT results on these patients were not included in the overall anxiety analysis. Thus the readers of this review will see sedation evaluation in 107 of 110 patients or 97.3%, while other evaluations will vary with the availability of data. All of this seems quite reasonable to this reviewer.

Sedation was evaluated exactly as for pooled protocol 2198A, already summarized. Briefly: intermediate ratings of 3 & 4, which stand for awake and drowsy (3) and asleep but easily responds to questions or commands in a normal tone of voice (4) are most desirable.

Induction was with thiopental intravenously, 3 mg/kg to start with.

Vital signs were studied as for 2198A.

RESULTS:

Sedation evaluation can best be judged from Tables 2, 3 & 4, and Figure (graph) 1 of the sponsor's summary, rearranged and reproduced for the next several pages:

TABLE 2 - MEAN DEGREE OF SEDATION

Observations	Mean Sedation Score [†]								
	N	Midazolam 0.07 mg/kg			N	Hydroxyzine 1.0 mg/kg			N
Baseline	101	5.0	-	101	5.0	-	103	5.0	-
15 Minutes	101	4.3	(-0.7)**	101	4.3	(-0.2)	105	4.9	(-0.1)
30 Minutes	100	3.7	(-1.3)**	99	4.4	(-0.5)*	102	4.7	(-0.3)
45 Minutes	91	3.5	(-1.5)**	94	4.1	(-0.9)*	98	4.6	(-0.4)
60 Minutes	73	3.5	(-1.5)*	84	4.0	(-1.0)*	78	4.7	(-0.3)

[†]Sedation Scale: 5=Hyperactive; 3=Awake/Alert; 2=Awake/Drowsy;
 1=Asleep/Easily responds to verbal commands;
 0=Asleep/Difficult response to verbal commands;
 -1=Asleep/No response to verbal commands

*Probability <0.05 (Analysis of covariance, one-sided vs placebo)
 **Probability <0.05 (Analysis of covariance, two-sided vs hydroxyzine)

TABLE 4

NUMBER AND PERCENT OF PATIENTS EITHER
 AWAKE/DROWSY OR ASLEEP/EASILY AROUSED

Observation Time	Midazolam		Hydroxyzine		Placebo	
	N	%	N	%	N	%
15 Minutes	46	45.5**	19	18.3	14	13.3
30 Minutes	54	54.0**	49	49.5*	25	24.5
45 Minutes	61	67.0*	61	64.9*	29	29.5
60 Minutes	51	69.9*	57	67.9*	18	23.1

*Probability <0.05 vs placebo (Mantel-Haenszel procedure)
 **Probability <0.05 vs hydroxyzine (Mantel-Haenszel procedure)

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Figure 1
 MEAN (±S.D.) DEGREE OF SEDATION
 PROTOCOL No. 2199A - POOLED RESULTS

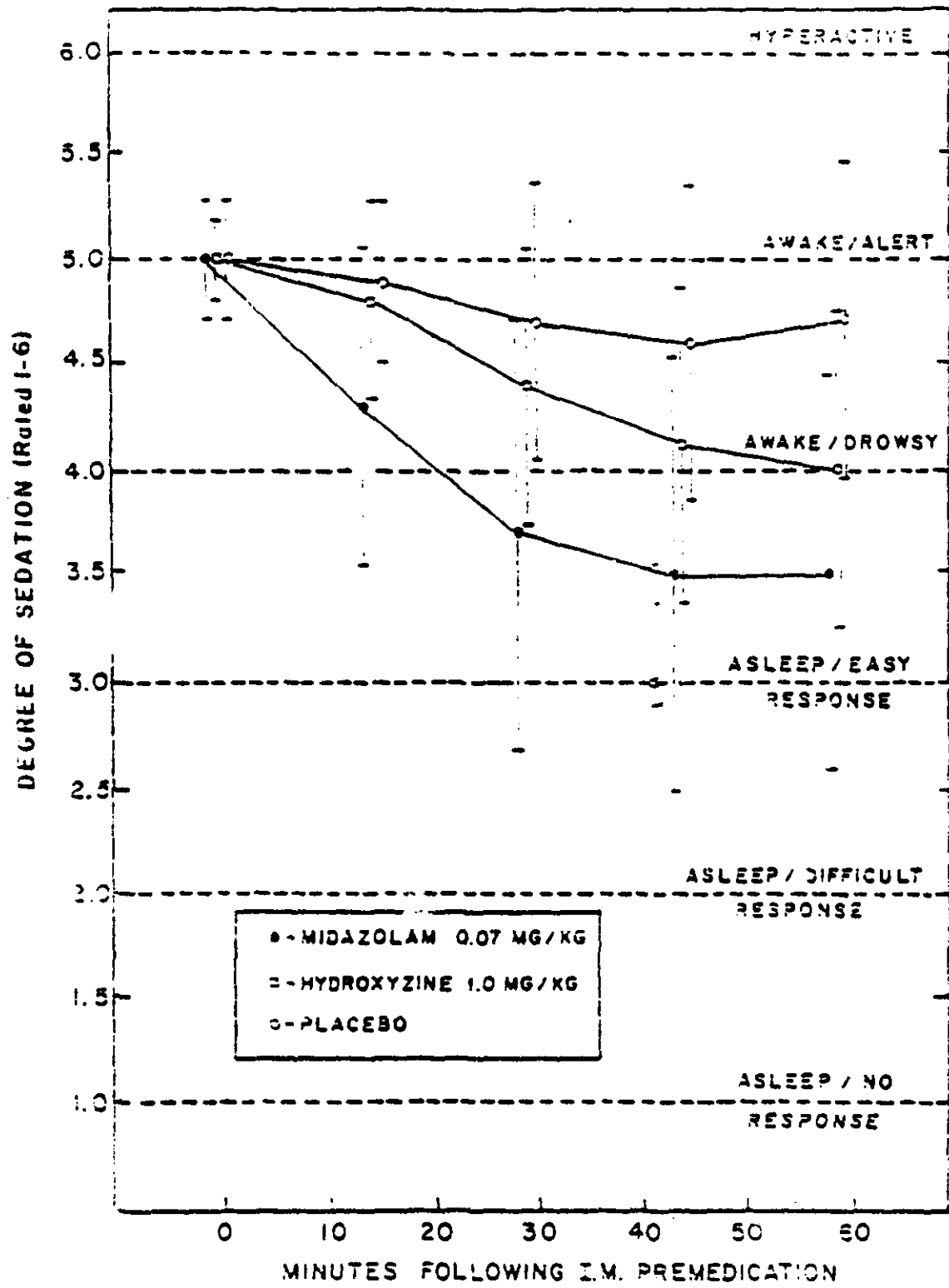


Table 3 and 4 illustrate the rapid onset of sedation among patients who received midazolam. After 15 minutes of premedication, just less than half (46/101 pts) of the midazolam group were either drowsy or asleep. Similar activity with hydroxyzine treatment was not observed until 30 minutes post-treatment. By comparison, 14 of the 105 placebo-treated patients (13.3%) were drowsy and only two of these patients were asleep.

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TABLE 3 - LEVELS OF SEDATION

Sedation Score	Observation Times (No.)									
	Baseline		15		30		45		60	
	N	%	N	%	N	%	N	%	N	%
Midazolam 0.07 mg/kg (N = 102)										
5 - Hyperactive	3	3.0	1	1.0	-	-	-	-	-	-
3 - Awake/Alert	33	92.1	52	51.5	23	23.0	13	14.3	0	0.0
4 - Awake/Drowsy	3	3.0	29	28.7	39	39.0	45	49.5	32	43.3
3 - Asleep/Easy Response*	-	-	17	16.3	25	25.0	16	17.5	19	25.0
2 - Asleep/Difficult Response*	-	-	2	2.0	9	9.0	10	11.0	3	11.0
1 - Asleep/No Response*	-	-	-	-	4	4.0	7	7.7	4	5.5

Sedation Score	Observation Times (No.)									
	Baseline		15		30		45		60	
	N	%	N	%	N	%	N	%	N	%
Hydroxyzine 1.0 mg/kg (N = 101)										
5 - Hyperactive	2	2.0	1	1.0	-	-	1	1.1	-	-
3 - Awake/Alert	36	95.0	91	80.1	48	48.5	29	29.3	24	28.6
4 - Awake/Drowsy	3	3.0	15	14.9	41	41.4	45	47.9	37	44.0
3 - Asleep/Easy Response*	-	-	4	4.0	3	3.1	16	17.0	20	23.3
2 - Asleep/Difficult Response*	-	-	-	-	2	2.0	4	4.3	3	3.5
1 - Asleep/No Response*	-	-	-	-	-	-	-	-	-	-

Sedation Score	Observation Times (No.)									
	Baseline		15		30		45		60	
	N	%	N	%	N	%	N	%	N	%
Placebo (N=105)										
5 - Hyperactive	3	4.8	2	1.9	1	1.0	4	4.1	5	7.7
3 - Awake/Alert	9	92.4	99	84.3	75	73.5	63	64.3	32	66.7
4 - Awake/Drowsy	2	1.9	12	11.4	18	17.5	17	17.3	12	15.4
3 - Asleep/Easy Response*	1	1.0	2	1.9	7	6.9	12	12.2	6	7.7
2 - Asleep/Difficult Response*	-	-	-	-	1	1.0	2	2.0	2	2.5
1 - Asleep/No Response*	-	-	-	-	-	-	-	-	-	-

* To standard questions

All of the patients rated 1 (asleep with no response to commands or questions in a normal tone of voice) were from Raymond Miller's study. There were seven such patients and these seven patients were so rated a total of 13 serial evaluations, 4 at 60 minutes, 5 at 45 minutes, 3 at 30 minutes and 1 at 75 minutes. I obtained the case numbers from Karen Church of ROCHE and checked the microfiche for each of these cases. The case reports revealed no patient management problems related to oversedation; the rating of 1 was never associated with a clinical judgement that an adverse reaction had taken place. All of these patients completed serial AVAT testing, often at the same time that they were rated asleep with no response to questions in a normal tone of voice. It seems that the person gathering the data really spoke softly while conducting this part of the test, as should be. This reviewer feels that this check of 7 case reports does much to support safety of the IM dose of midazolam 0.07 mg/kg for the INDICATION of pre-anesthetic medication; it is also obvious that these data support efficacy (sedation evaluation).

AVATs TESTING:

Definitive evaluation is being conducted by the staff of HFN-120, therefore, the following highlights are for acknowledgement of results only:

Patients premedicated with midazolam and hydroxyzine scored lower at one hour evaluation or when called for surgery (if "last observation" was in less than 60 minutes) than did placebo patients; this means that they manifested less preoperative anxiety or apprehension, under the conditions of this experiment. There was no difference between midazolam and hydroxyzine in this regard.

Table 5 from the sponsor's summary, reproduced below, shows mean AVAT score for all testings. Figure 2 (graph), reproduced on the next page, shows AVAT testing only for those patients who were not called for surgery within one hour of pre-anesthetic medication (Figure 2 is also from the sponsor's summary):

TABLE 5

ANXIETY VISUAL ANALOG TEST (AVAT)

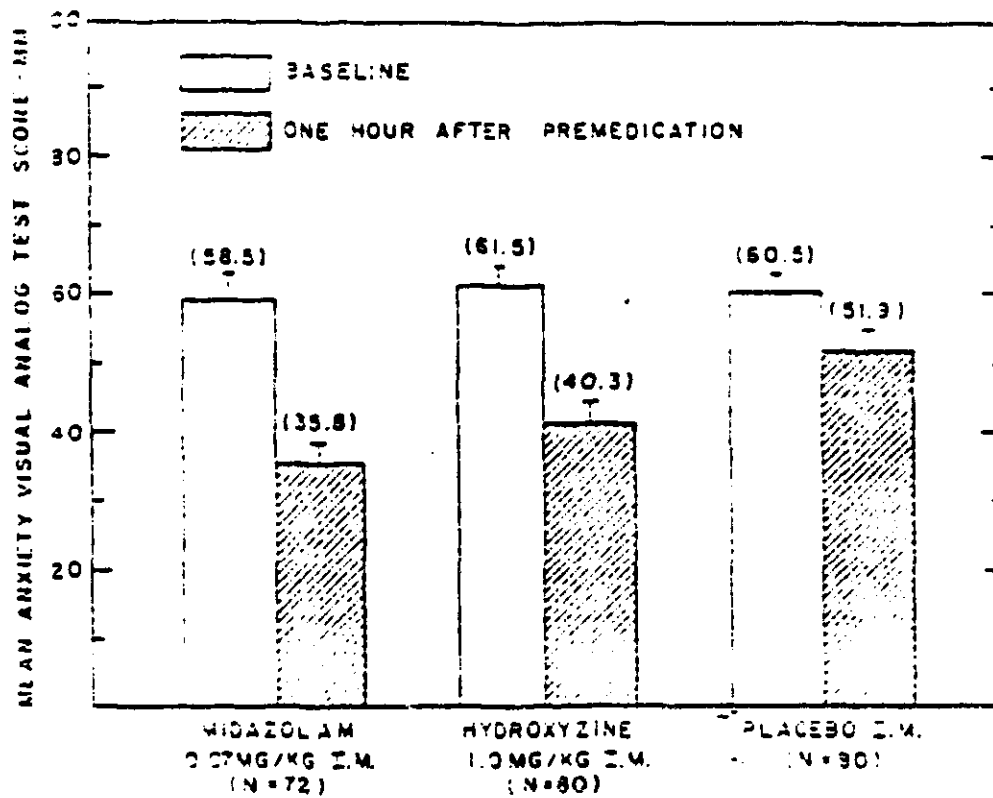
Mean AVAT Score[†] (Δ)

Observation Time	N	Midazolam	N	Hydroxyzine	N	Placebo
Baseline	33	59.5	39	52.3	103	52.3
60 Minutes	72	35.9 (-22.7)*	80	40.3 (-21.2)*	90	51.9 (-3.5)
Last Observation	98	41.2 (-18.3)*	99	41.9 (-20.9)*	103	54.9 (-7.5)

[†] Anxiety scale: 0 mm = No anxiety; 100 mm = Maximum anxiety

* Probability < 0.05 (Analysis of covariance, one-sided vs placebo)

Figure 2
 MEAN (+S.E.M.) ANXIETY VISUAL ANALOG TEST SCORES
 PROTOCOL No.2199A - POOLED RESULTS



INDUCTION:

Mean time to induction was faster in patients premedicated with midazolam and hydroxyzine than with placebo. Thiopental requirements were also less in patients premedicated with active drug. This can be seen from Table 6 of the sponsor's summary, reproduced below:

TABLE 6
 INDUCTION OF ANESTHESIA

	Midazolam 0.07 mg/kg IM	Hydroxyzine 1.0 mg/kg IM	Placebo IM
<u>Number of Patients</u>	98	100	103
<u>Time to Induction (sec)</u>			
Mean (+S.E.M.)	96.9 (+7.4)*	83.2 (+3.4)*	125.9 (+6.5)
Median	60	60	75
Range	33 - 660	20 - 330	25 - 350
<u>Thiopental Induction Dose (mg/kg)</u>			
Mean (+S.E.M.)	3.6 (+0.1)*	3.3 (+0.04)*	4.2 (+0.1)
Median	3.0	3.0	3.5
Range	1.9 - 9.1	2.3 - 6.3	2.3 - 8.9

*Probability <0.05 (Analysis of variance; one-sided vs. placebo)

SAFETY:

Transient pain on injection was reported in 9/102 patients receiving midazolam (8.8%). Only one of these patients complained of pain at the followup (24 hours only, recovering afterwards before next followup). All but one of these 9 cases were from Dr. Vinik's study. Forty eight of the 102 hydroxyzine patients, or 47.1%, manifested pain on injection (23/102) and/or residual pain at the 24 and 48 hour evaluation (33/102); in the 33 patients with residual pain 24 or more hours later, duration of this pain ranged from 2 to 28 days (median 4 days); these effects were generally judged to be mild to moderate in severity. One placebo patient manifested pain following injection.

One placebo patient out of 105 (0.9%) manifested a mild face rash on the first and second postoperative day.

One midazolam patient manifested sinus tachycardia on induction; the patient was judged adequately anesthetized at the time and thus the clinician felt that there was a remote possibility that this had some association with administration of midazolam.

One midazolam patient manifested a euphoric episode, with inappropriate laughter, during the preanesthetic evaluation period; the patient's report was that of feeling drunk. One placebo premedicated patient manifested an unexplained episode of auditory hallucinations during emergence from anesthesia; this patient did not receive ketamine during the procedure (anesthetic maintenance was left up to the individual anesthesiologists in this protocol).

Hematological and biochemical screening, before and at least once after anesthesia and surgery, was performed in 287 of 310 cases. The summary does not mention timing of postoperative samples but a spot check of case reports on microfiche (study of AHG) reveals that the preoperative sample was usually taken the day before surgery and the postoperative sample was usually taken either on the first or the second postoperative day. These data revealed no changes reasonably attributable to the administration of midazolam or hydroxyzine. For instance, the highest postoperative SGOT was 191 in a patient who received midazolam and who underwent gastropasty; the next highest was an SGOT of 133 in a patient premedicated with hydroxyzine who underwent a laminectomy. Seven hydroxyzine patients, 10 midazolam patients and 8 placebo patients had pre-surgical SGOT values within normal limits and manifested an increase beyond normal limits at the time of postoperative evaluation.

The most useful information about vital sign changes is derived from data restricted to the time between premedication and call to surgery. This allows about one hour of evaluation following test drug administration and before other drugs are administered. Obviously, preoperative apprehension and the activity of hospital personnel can also affect vital signs during this test period; this should be kept in mind while evaluating these data.

2199A---page Eight-----

The table below was prepared by me with the assistance of Karen K. Church of RCHM. The remarks made for summary of 2198A also apply here:

VITAL SIGN CHANGES BETWEEN TIME OF INJECTION AND CALL TO SURGERY

	Mild Increase (%)	Mild Decrease (%)	Moderate Increase (%)	Moderate Decrease (%)	Severe Increase (%)
I. PULSE					
Midazolam (n = 102)	8 (7.8)	7 (6.9)	0 (0)	2 (2)	0 (0)
Hydroxyzine (n = 102)	2 (2)	15 (14.7)	3 (2.9)	1 (1)	1 (1)
Placebo (n = 106)	3 (2.8)	6 (5.7)	6 (5.7)	4 (3.8)	2 (1.9)
II. MEAN ARTERIAL PRESSURE					
Midazolam	6 (5.9)	6 (5.9)	2 (2)	2 (2)	0 (0)
Hydroxyzine	6 (5.9)	5 (4.9)	1 (1)	0 (0)	0 (0)
Placebo	7 (6.6)	2 (1.9)	3 (2.8)	0 (0)	0 (0)

Through this scattering of vital sign changes, very little difference between groups is seen. No midazolam patients manifested any severe changes (as before, defined as changes of 50% or more from baseline or changes requiring treatment—see summary for 2198A). More hydroxyzine patients tended to manifest decreased heart rate. Less placebo patients tended to manifest decreased mean arterial pressure.

A word about calculating mean arterial pressure is in order. For all midazolam studies, III and IV, mean arterial pressure was calculated according to the formulae:

Mean arterial pressure = Diastolic pressure plus 1/3 of the pulse pressure

The pulse pressure = $\frac{\text{Systolic blood pressure} - \text{diastolic b.p.}}{3}$

DIFFERENCES BETWEEN INDIVIDUAL STUDIES FOR PROTOCOL 2199A:

There were few differences between investigators, and, in the opinion of this clinical reviewer, none that precluded making use of the pooled data summary. Dr. Slavic's patients had a longer thiopental induction time than did other investigators. Dr. Miller's patients were generally judged more sedated than those of other investigators (already discussed). Dr. Vinik requested more leeway in patient selection and was permitted to include ASA Status III patients; there were four such patients. Eight of the 9 patients who manifested pain immediately after injection of IM midazolam were from the study of Dr. Vinik. Buddy Giesecke was generally more prone to report pain immediately after injection; when the code was broken it turned out that almost all of these cases involved injection of hydroxyzine (16/30 or 53%); he reported one case, out of 30, for each of the other two test groups (midazolam and placebo, each 3% of total cases).

There were differences between investigators regarding AVATs. Giesecke and colleagues handed in data which when analyzed revealed no difference between treatment groups regarding AVATs. Dr. Miller's data revealed a difference between midazolam and placebo, in favor of midazolam. Dr. Vinik's data revealed a difference between midazolam and placebo in favor of midazolam, and a difference between midazolam and hydroxyzine in favor of midazolam. There are insufficient data from Dr. Slavic's study on which to make conclusions. It is obvious that non-drug factors, especially the skill of the investigator(s) and other hospital personnel in handling patients awaiting call to surgery, can also affect the severity of preoperative anxiety or apprehension; indeed, the example cited may often be the deciding factor. Definitive review of AVATs will be by HFN-120 Staff.

The 310 patients were derived as follows:

Giesecke—90 patients (90 with data analyzed)
Miller—90 patients (90 with data analyzed)
Vinik—100 patients (97 with data analyzed)
Slavic—30 patients (30 with data analyzed)

Individual Study No. 2325A

Theodore C. Smith, M.D., Loyola Univ. Medical Center, Maywood, Illinois
 Dr. Smith is an Anesthesiologist especially noted for his pulmonary research.

This study has previously been summarized; see pages 29 through 31 of _____ and
 Summary Dated 24 August 1982.

adult

All that need be stated here is that 9 healthy male volunteers participated in a double-blind randomized crossover study of the ventilatory response to carbon dioxide after: 1. midazolam 0.07 mg/kg IM plus placebo IM, 2. morphine 0.14 mg/kg IM plus placebo IM, 3. morphine 0.14 mg/kg IM plus midazolam 0.07 mg/kg IM. Volunteers were judged free of drugs, except for test drugs. Midazolam IM did not significantly depress the respiratory response to carbon dioxide stimulation and did not add to the depression of respiratory response to carbon dioxide noted after the administration of morphine IM. None of the subjects were oversedated, so no conclusions can be made about respiratory depression or lack of same in oversedated patients or subjects. It goes without saying that this does not speak for larger doses of midazolam, which were not tested.

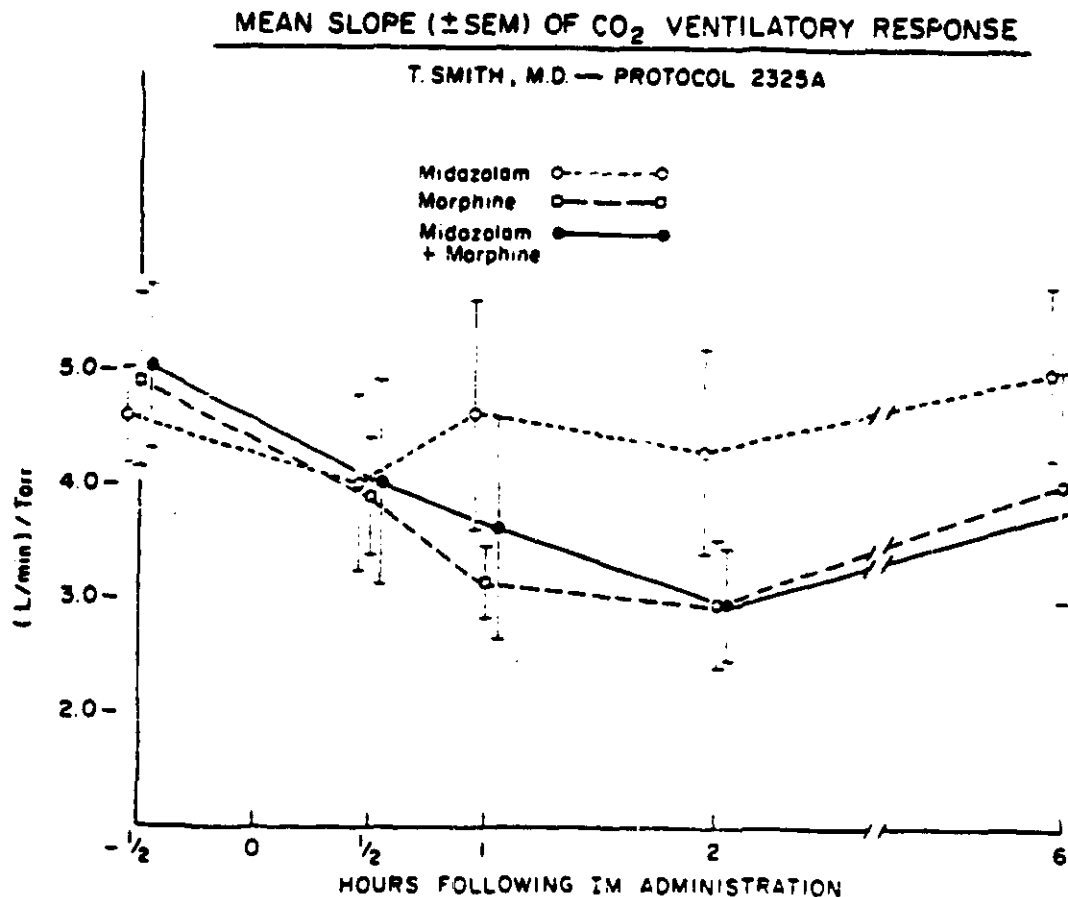
mild to moderate

Twenty two percent of the midazolam subjects manifested decreased pulse rate at some time during the six hours of testing, morphine 78%, both drugs together 5%. Twenty two percent of the midazolam subjects also manifested an increase in pulse rate, 11% for morphine and 0% for the combination. There were not ECG changes. One subject developed headaches when challenged with carbon dioxide. Pain at the injection site was noted once after administration of midazolam.

mild to moderate

For the record, the graph below (Figure 1) is from the sponsor's summary:

Figure 1



Protocol 2206A

Kai Reher, M.D., Dept. of Anes., Mayo Clinic, Rochester, MN

The objective of this ^{open} study was to determine the effects of midazolam maleate on the dynamic pulmonary compliance and pulmonary resistance, static pressure-volume relationship of the lung and on the maximal expiratory flow-volume relationship.

Tests were conducted in six healthy male volunteers, aged 25-31 years. Respiratory mechanics were studied before and after the administration of midazolam. The initial dose, aimed at maintaining a sedated but awake status, was 0.121 mg/kg, but after the first two cases this was reduced to 0.09 mg/kg. Sedation was maintained by an intravenous infusion of midazolam maleate at a rate of 0.025 mg/minute in the first two cases and 0.05 mg/minute in the remaining four cases.

An esophageal balloon was inserted and inflated with 0.8 ml of air; this was used to obtain esophageal pressure (Pes) in lieu of intrapleural pressure. Lung volumes (TLC-total lung capacity, FRC-functional residual capacity and RV-residual volume) were measured by a body plethysmographic technique. The FRC was taken as the volume of gas contained in the thorax when airway pressure equaled atmospheric pressure. Airway pressure was recorded at the mouth (Pao). Transpulmonary pressure (Ptp) was taken as the difference between ~~transpulmonary~~ Pao and Pes.

Dynamic pulmonary compliance and resistance were derived from measurements taken during 5 minutes of quiet breathing. Static pressure and resistance measurements required a maximum inspiration and then intermittent breath holding for 3 seconds during subsequent passive expiration (lung deflation). Static pressure-volume curves were obtained from the simultaneous measurements of the static pressure and volume during passive deflation. From these curves the static lung compliance was measured between 45-55% of awake TLC and static lung recoil was determined at 50% awake TLC. Flow-volume curves were obtained with the subject forcibly exhaling from TLC to RV. Peak expiratory flow (PEF) and maximum expiratory flow at 50% awake TLC (Vmax) were measured from composite flow-volume curves.

Calculations: Compliance (L/cm H₂O) = $\frac{\text{Change in lung volume (L)}}{\text{Change in transpulmonary pressure (cmH}_2\text{O)}}$

Resistance (cmH₂O/L/second) = $\frac{\text{Pressure difference (cmH}_2\text{O)}}{\text{Volume flow (L/second)}}$

RESULTS:

The following tables and figures, ~~presented~~ from the sponsor's summary, are concerned with the results of this study. These data have led to conclusions that sedation with midazolam did not affect the functional residual capacity or residual volume significantly. Pulmonary resistance and static recoil were also not affected by midazolam sedation. Total lung capacity and peak expiratory flow decreased significantly, perhaps because of the sedation. Vmax was greater during the sedated state than the awake state. Static compliance increased during the sedated state induced by midazolam. The sponsor concluded that midazolam does not increase the work of breathing and does not cause bronchoconstriction.

Protocol 2206A

Kai Rehder, M.D., Dept. of Anes., Mayo Clinic, Rochester, MN

The objective of this ^{study} was to determine the effects of midazolam maleate on the dynamic pulmonary compliance and pulmonary resistance, static pressure-volume relationship of the lung and on the maximal expiratory flow-volume relationship.

Tests were conducted in six healthy male volunteers, aged 25-31 years. Respiratory mechanics were studied before and after the administration of midazolam. The initial dose, aimed at maintaining a sedated but awake status, was 0.121 mg/kg, but after the first two cases this was reduced to 0.09 mg/kg. Sedation was maintained by an intravenous infusion of midazolam maleate at a rate of 0.025 mg/minute in the first two cases and 0.05 mg/minute in the remaining four cases.

An esophageal balloon was inserted and inflated with 0.8 ml of air; this was used to obtain esophageal pressure (Pes) in lieu of intrapleural pressure. Lung volumes (TLC-total lung capacity, FRC-functional residual capacity and RV-residual volume) were measured by a body plethysmographic technique. The FRC was taken as the volume of gas contained in the thorax when airway pressure equaled atmospheric pressure. Airway pressure was recorded at the mouth (Pao). Transpulmonary pressure (Ptp) was taken as the difference between ~~Pao and Pes.~~ Pao and Pes.

Dynamic pulmonary compliance and resistance were derived from measurements taken during 5 minutes of quiet breathing. Static pressure and resistance measurements required a maximum inspiration and then intermittent breath holding for 3 seconds during subsequent passive expiration (lung deflation). Static pressure-volume curves were obtained from the simultaneous measurements of the static pressure and volume during passive deflation. From these curves the static lung compliance was measured between 45-55% of awake TLC and static lung recoil was determined at 50% awake TLC. Flow-volume curves were obtained with the subject forcibly exhaling from TLC to RV. Peak expiratory flow (PEF) and maximum expiratory flow at 50% awake TLC (Vmax) were measured from composite flow-volume curves.

Calculations: Compliance (L/cm H₂O) =
$$\frac{\text{Change in lung volume (L)}}{\text{Change in transpulmonary pressure (cmH}_2\text{O)}}$$

Resistance (cmH₂O/L/second) =
$$\frac{\text{Pressure difference (cmH}_2\text{O)}}{\text{Volume flow (L/second)}}$$

RESULTS:

The following tables and figures, ~~based~~ from the sponsor's summary, are concerned with the results of this study. These data have led to conclusions that sedation with midazolam did not affect the functional residual capacity or residual volume significantly. Pulmonary resistance and static recoil were also not affected by midazolam sedation. Total lung capacity and peak expiratory flow decreased significantly, perhaps because of the sedation. Vmax was greater during the sedated state than the awake state. Static compliance increased during the sedated state induced by midazolam. The sponsor concluded that midazolam does not increase the work of breathing and does not cause bronchoconstriction.

		TABLE - 3						
		LUNG VOLUMES (LITERS)						
		Subj.	Subj.	Subj.	Subj.	Subj.	Subj.	
		#1	#2	#3	#4	#5	#6	Mean $\pm$ SE
FRC (L) (Functional Residual Capacity)	Awake state	2.95	3.15	1.86	2.26	2.44	2.03	2.45 $\pm$ 0.21
	Sedated state	2.62	2.82	1.91	2.29	2.29	2.02	2.33 $\pm$ 0.14
	Difference	0.33	0.33	-0.05	-0.03	0.15	0.01	0.12
RV (L) (Residual Volume)	Awake state	1.81	2.01	1.19	1.85	1.88	1.42	1.69 $\pm$ 0.13
	Sedated state	1.71	2.10	1.35	1.67	1.60	1.59	1.67 $\pm$ 0.10
	Difference	0.10	-0.09	-0.16	0.18	-0.28	-0.17	0.02
TLC (L) (Total Lung Capacity)	Awake state	8.57	8.05	5.52	6.64	7.68	7.92	7.40 $\pm$ 0.46
	Sedated state	8.40	7.59	5.38	6.36	7.45	7.59	7.13 $\pm$ 0.44
	Difference	0.17	0.46	0.14	0.28	0.23	0.33	0.27*
Awake state - Prior to the initial bolus injection of midazolam								
Sedated state - During midazolam infusion, following the initial bolus injection								
*Difference is significant ($p < 0.05$)								

Dynamic Pulmonary Compliance and Resistance (Table 4)

The results are presented in Table 4. There were slight decreases or increases with a resultant increase in mean dynamic pulmonary compliance and a decrease in pulmonary resistance during the state of sedation induced by midazolam. These changes, however, were not statistically significant.

		Subj.	Subj.	Subj.	Subj.	Subj.	Subj.	Mean ± SE
		#1	#2	#3	#4	#5	#6	
Dynamic Compliance (L/cm H ₂ O)	Awake state	0.220	0.352	0.190	0.190	0.209	0.150	0.219 ± 0.03
	Sedated state	0.215	0.416	0.147	0.337	0.296	0.117	0.225 ± 0.05
	Difference	0.005	-0.064	0.043	-0.147	-0.087	0.033	-0.006
Resistance (cm H ₂ O/L/sec)	Awake state	3.33	1.88	2.87	5.45	3.67	7.66	4.14 ± 0.25
	Sedated state	2.78	1.71	3.87	7.28	3.18	4.73	3.93 ± 0.79
	Difference	0.55	0.17	-1.00	-1.83	0.49	2.93	0.21

(Statistically, the differences were not significant).

Static Lung Compliance and Static Recoil of Lung
(from Static Pressure-Volume Curves) (Table 5)

Sedation with midazolam increased the static lung compliance, and no significant change in the static recoil of lung was noted. This indicates that the sedation induced by midazolam did not increase the work of breathing. The results are listed in Table 5, and Figure 1 illustrates the mean lung pressure-volume curve for all 6 subjects.

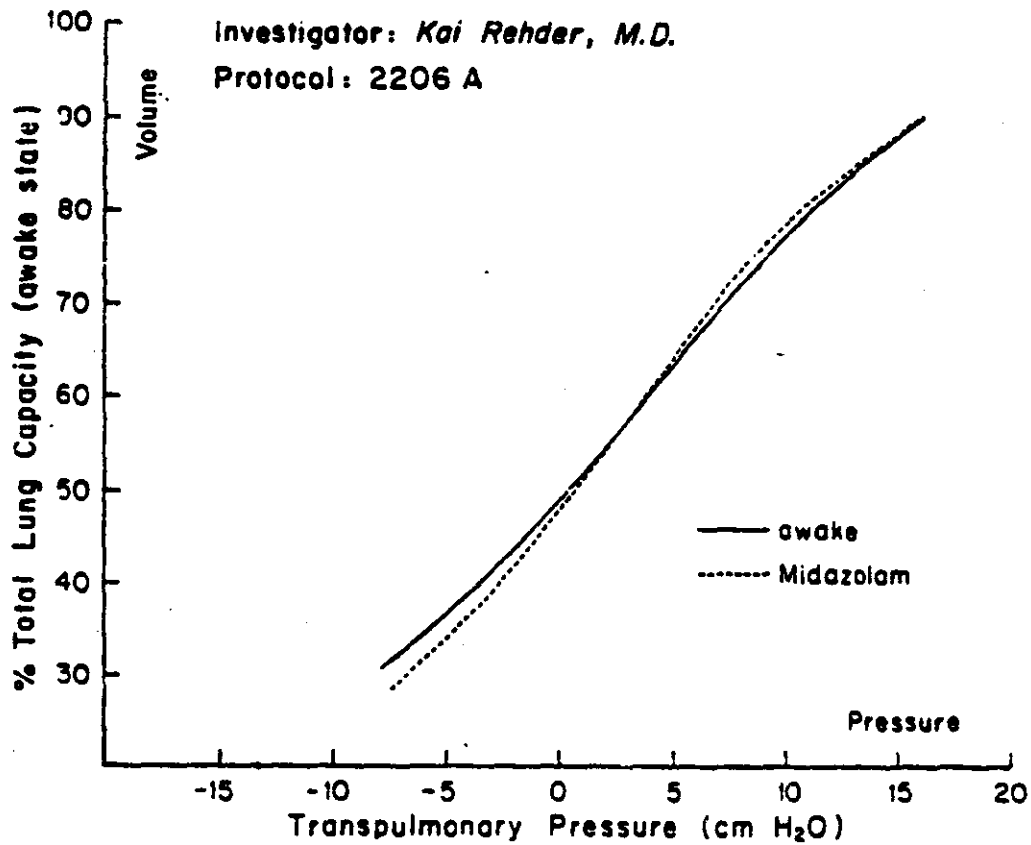
		Subj. #1	Subj. #2	Subj. #3	Subj. #4	Subj. #5	Subj. #6	Mean ± SE
<u>TABLE - 5</u>								
<u>STATIC PULMONARY COMPLIANCE AND STATIC RECOIL OF LUNG</u>								
Static recoil of lung at 50% Awake TLC (cm H ₂ O)	Awake state	2.4	0.9	2.3	-1.7	-0.9	-0.02	0.47 ± 0.69
	Sedated state	2.5	1.7	2.3	-0.9	-2.0	0.01	0.62 ± 0.75
	Difference	-0.1	-0.8	0	-0.8	1.1	-0.03	-0.15
Static compliance of lung between 45-55% Awake TLC (L/cm H ₂ O)	Awake state	0.267	0.164	0.197	0.141	0.248	0.255	0.212 ± 0.02
	Sedated state	0.306	0.288	0.197	0.154	0.284	0.330	0.260 ± 0.03
	Difference	-0.039	-0.124	0	-0.013	-0.036	-0.075	-0.048*
		*Difference is significant (p<0.05)						

FIGURE 1

Pressure-Volume Curve

Investigator: Kai Rehder, M.D.

Protocol: 2206 A



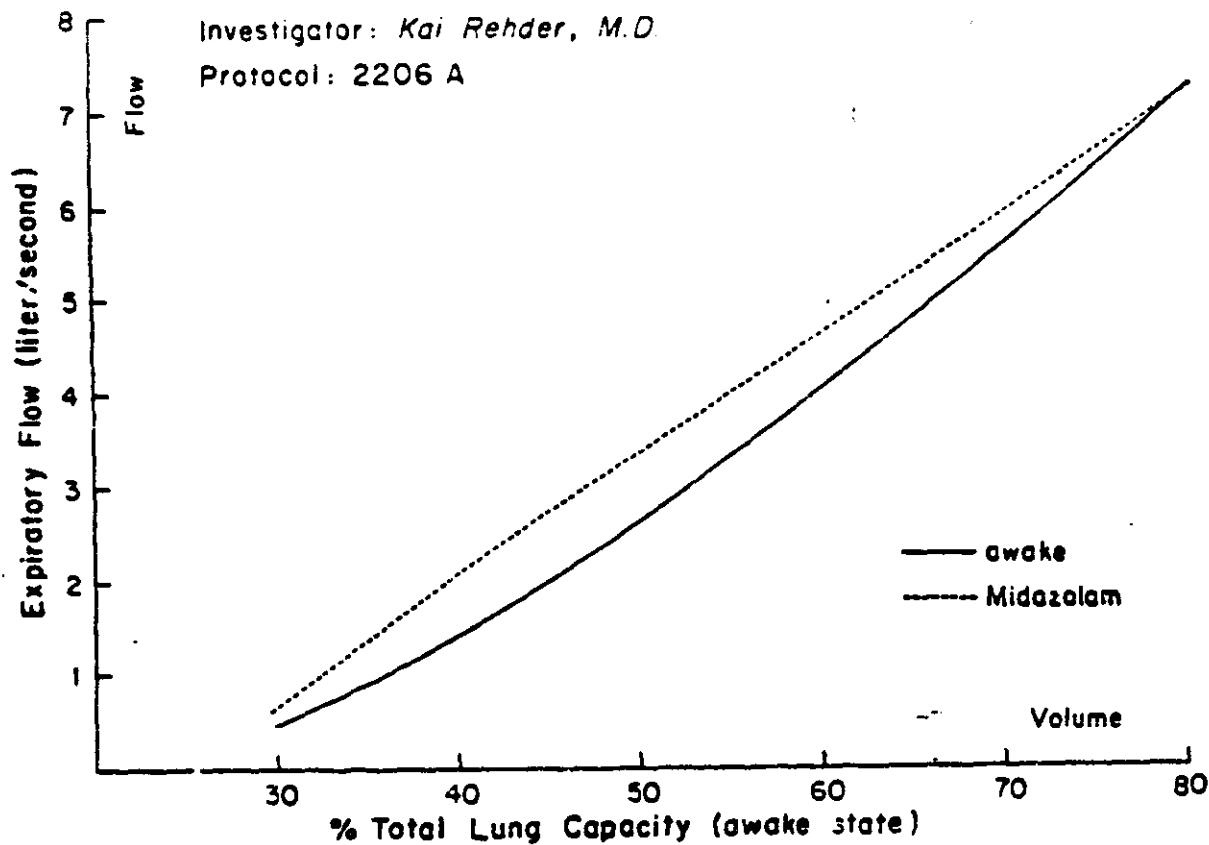
Expiratory Flow and Lung Volume
(Flow-Volume Curves) (Table 6)

The maximum expiratory flow at 50% awake TLC ($\dot{V}_{max}$), as seen in Table 6, increased significantly during the sedated state induced by midazolam. This suggests that midazolam did not cause any airway narrowing. The results also showed a significant reduction in the peak expiratory flow during the sedated state; however, according to the investigator, this was probably caused by a loss of volition in the sedated subjects. Figure 2 (flow-volume curve) illustrates that at the same lung volume (50% TLC), the expiratory flow was greater during the sedated state induced by midazolam than the measurement obtained during the awake state.

		<u>TABLE - 6</u>						
		<u>EXPIRATORY FLOW AND LUNG VOLUME</u>						
		Subj.	Subj.	Subj.	Subj.	Subj.	Subj.	
		<u>#1</u>	<u>#2</u>	<u>#3</u>	<u>#4</u>	<u>#5</u>	<u>#6</u>	<u>Mean ± SE</u>
Maximum expiratory flow at 50% Awake TLC ($\dot{V}_{max}$) (L/sec)	Awake state	2.88	1.19	3.20	1.35	4.73	2.24	2.60 ± 0.54
	Sedated state	2.94	3.01	3.88	2.25	5.49	2.88	3.41 ± 0.47
	Difference	-0.06	-1.82	-0.68	-0.90	-0.76	-0.64	-0.81*
Peak expiratory flow (L/sec)	Awake state	9.05	11.24	6.49	8.99	10.66	8.95	9.26 ± 0.70
	Sedated state	7.11	9.16	6.04	7.36	9.13	7.98	7.80 ± 0.50
	Difference	1.94	2.26	0.45	1.63	1.53	0.97	1.46*

*Difference is significant (p<0.05)

FIGURE 2
Flow-Volume Curve



SAFETY:

slight to moderate

Subjects tended to have pulse rate increase after injection of midazolam. This was a relatively transient observation and never required treatment. Case No. 2 is listed as moderately-severe increase in pulse (perhaps not following the usual check list code), so I checked the case report; it turns out that pre-test drug administration pulse was 60/minute and that it rose to 100/minute before settling back. Sometimes blood pressure fell slightly at the same time, but it was really slight, like from 122/70 to 110/68. Subject No. 6 is listed as having transient hiccoughs over the time period of approximately 2 hours after test drug administration; these occasional hiccoughs obviously did not interfere with testing. There is no information on hiccoughs on the microfiche case report, but it is cited in the sponsor's summary.

Telephone contact with the volunteers at a later date revealed no claim of irritation at the intravenous site.

Protocol 2138

Theodore C. Smith, M.D. & Jeffrey Gross, M.D., Dept. of Anes., Univ. of Pennsylvania, Philadelphia.

This was an evaluation of the ventilatory effects of ^{intravenous} midazolam maleate, ^{intravenous} thiopental sodium and intravenous diazepam on ventilatory response to carbon dioxide stimulation. The study was really in three parts: 1. A double-blind crossover comparison of midazolam maleate and thiopental sodium in eight adult male volunteers, aged 20-49 years. 2. An open ~~evaluation~~ evaluation of the ventilatory response to diazepam intravenous in eight similar volunteers, aged 19-50 years. Two volunteers who participated in part one also participated in part two, as did six new volunteers. 3. A double-blind crossover comparison of midazolam maleate and thiopental sodium in seven male volunteers with chronic obstructive pulmonary disease (COPD), aged 43-67 years. One patient in this last group was excluded from analysis because of severe coughing throughout all tests, and this was the only exclusion. such Signs and symptoms used to select COPD patients included: 1. Long smoking histories, 2. Chronic productive cough, 3. Increased anteroposterior chest dimensions compatible with COPD, & 4. Peak expiratory flow rate (PEFR) of less than 400 liters per minute.

Part I:

Subjects breathed 50% oxygen in nitrogen during the testing. Variable carbon dioxide absorption was employed to control the end tidal PCO_2 within 1.5 mmHg (+). After carbon dioxide response curves were obtained, end tidal PCO_2 was held at 46 or 58 mmHg in alternate subjects, to compensate for any effect of study sequence. Thiopental 3.5 mg/kg or midazolam 0.2 mg/kg was injected intravenously over 15 seconds. Minute ventilation was measured every 30 seconds for the first five minutes, and at increasing intervals thereafter until the study was terminated at 15 minutes. Subjects were then allowed to recover for 4 hours before repeating the study with an end tidal PCO_2 of 58 or 46, whichever had not already been tested for that particular subject. To account for the effects of residual midazolam or thiopental, the dose administered 4 hours later was reduced by 5% (3.3 mg/kg for thiopental & 0.19 mg/kg for midazolam).

A minimum of 72 hours was allowed to elapse before subjects were re-tested with whichever drug they had not already been tested with.

Part II:

The methodology was similar to Part I. Subjects were not blinded. The test drug was diazepam 0.4 mg/kg intravenously, administered only once per day under the influence of either 46 or 58 mmHg end-tidal PCO_2 . The study was repeated after allowing at least 72 hours to recover from the influence of diazepam, at either end tidal PCO_2 of 46 or 58 (whichever had not been tested in that particular subject). In this part of the study, in deference to the longer action of diazepam as understood by the investigators, minute ventilation was measured at increasing intervals for 30 minutes rather than the 15 minutes allowed for in Part I.

Part III:

The methodology was virtually the same as for Part I, except that these volunteers had COPD. In deference to the condition of these patients, minute ventilation data was gathered at increasing intervals over 20 minutes rather than the 15 minutes allowed for in Part I. Doses of midazolam and thiopental were the same as for Part I.

Data were also gathered serially on state of consciousness during the study period. Criteria and results will be obvious from Table 2, reproduced as part of this review (from sponsor's summary).

Approximately one week after the study, each subject was contacted either by phone or personally for evaluation of the site of the intravenous infusion.

$$\text{Slope (L/minute/mmHg)} = \frac{\text{Minute volume (L/minute)}}{\text{PETCO}_2 \text{ (mmHg)}}$$

Time to minimum mean slope was determined, as was time to return to 80% of baseline slope. Since this involved lots of calculations performed later, return to exactly 80% was not always determinable.

RESULTS (NORMAL SUBJECTS):

One minute after thiopental, the slope dropped from 1.83 L/minute/mmHg to a low of 1.23 L/minute/mmHg. By 3 minutes after injection the slope had returned to 1.54 L/minute/mmHg or 84% of control.

and one-half (3.5)

Three minutes after midazolam, the slope dropped from 1.82 L/minute/mmHg to a low of 0.93 L/minute/mmHg. At the end of the test period, 15 minutes after injection, the slope had returned to only 76% of control or 1.39 L/minute/mmHg.

Three minutes after diazepam, the slope dropped from 2.38 L/minute/mmHg to a low of 1.19 L/minute/mmHg. At the end of the test period, 30 minutes after injection, the slope had returned to only 73% of control or 1.73 L/minute/mmHg.

With the doses employed in this study, thiopental had a shorter duration of ventilatory depression than either midazolam or diazepam in normal subjects.

RESULTS (COPD SUBJECTS):

One and one-half (1.5) minutes after thiopental injection, the mean slope dropped from 1.49 L/minute/mmHg to a low of 0.67 L/minute/mmHg. By 3 minutes after injection the slope had returned to 88% of control or 1.32 L/minute/mmHg.

Ten minutes after injection of midazolam, the mean slope dropped from control of 1.74 L/minute/mmHg to 0.35 L/minute/mmHg. When the test period had ended, 20 minutes after injection, the slope had risen to only 32% of control or 0.56 L/minute/mmHg.

For COPD subjects, thiopental had a shorter duration of depression of ventilation than did midazolam (at the doses employed).

To facilitate evaluation, figures and tables derived from the sponsor's summary are reproduced on the next several pages.

NORMAL SUBJECTS, MIDAZOLAM vs THIOPENTAL

Figure - 1a

CONSTRUCTED VENTILATORY RESPONSES AFTER
MIDAZOLAM IN NORMAL SUBJECTS

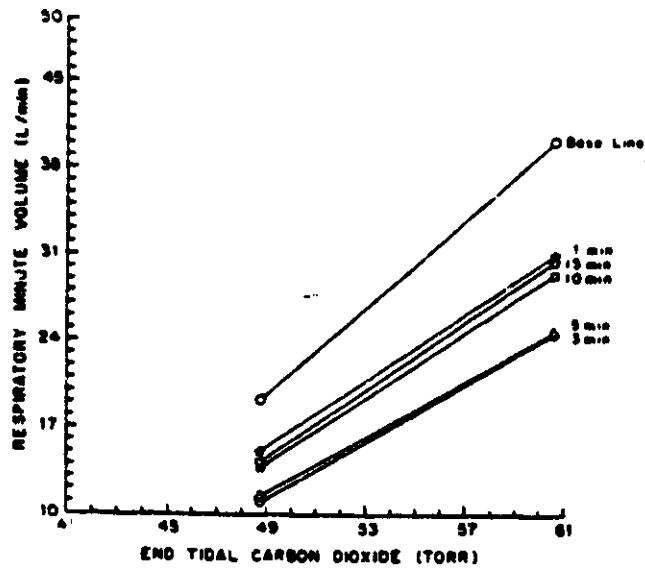


Figure - 1b

CONSTRUCTED VENTILATORY RESPONSES AFTER
THIOPENTAL IN NORMAL SUBJECTS

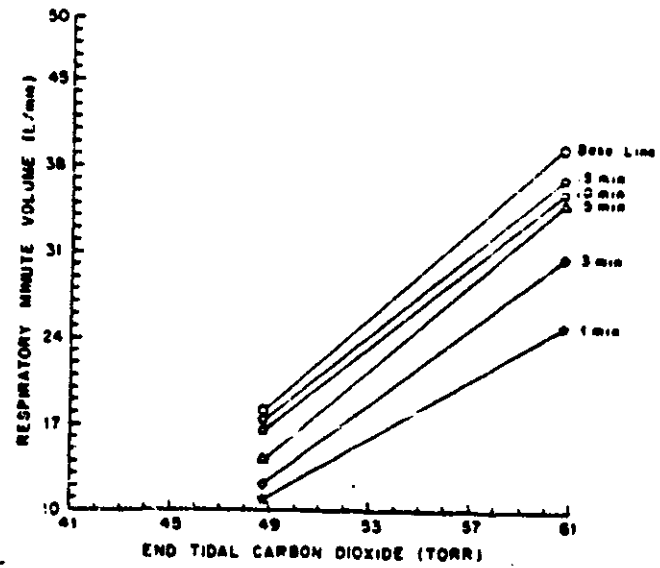
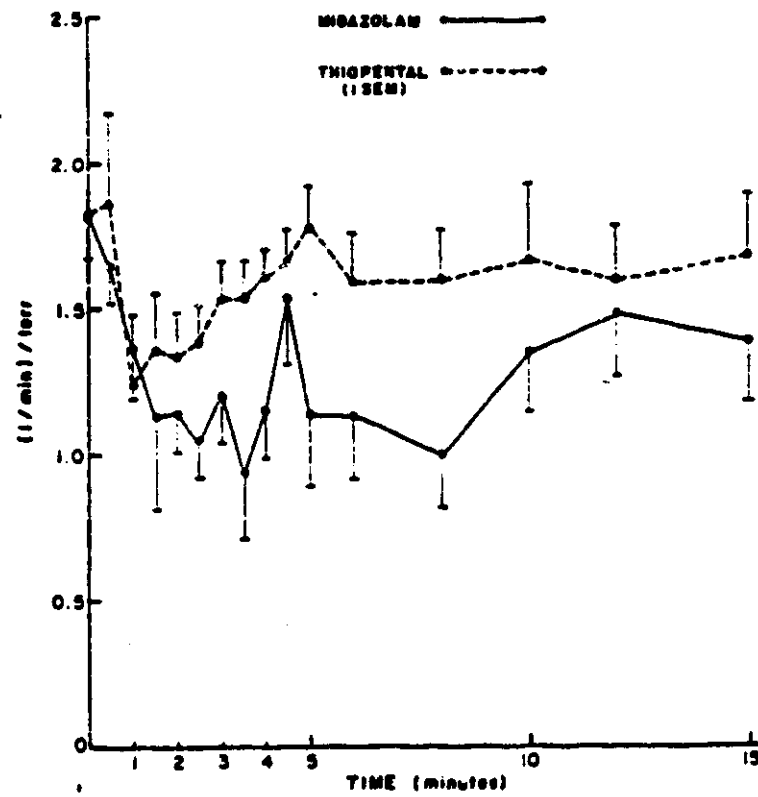


Figure 2

MEAN SLOPE OF CO₂ RESPONSE CURVE: NORMAL SUBJECTS (N=8)



NORMAL SUBJECTS, DIAZEPAM

Figure - 3

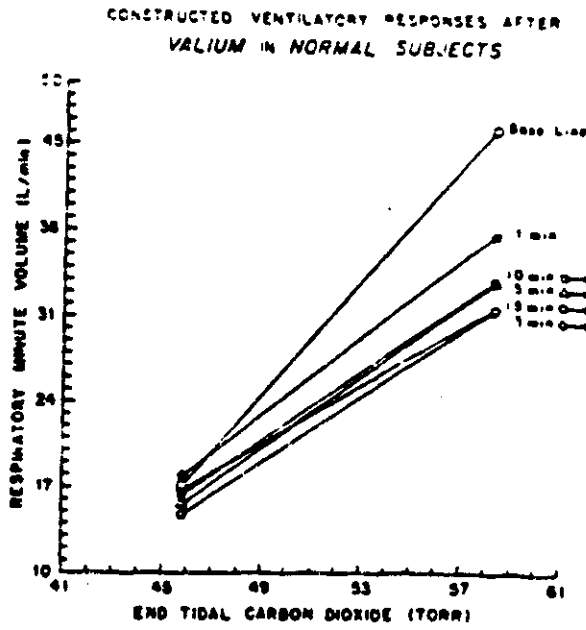
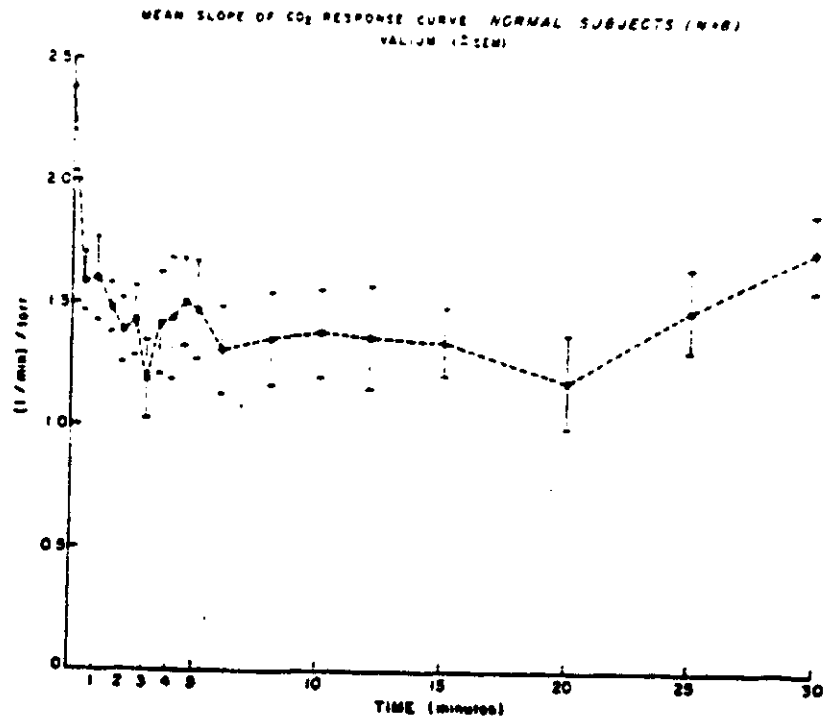


Figure 4



COPD SUBJECTS, MIDAZOLAM vs THIOPENTAL

Figure - 5a

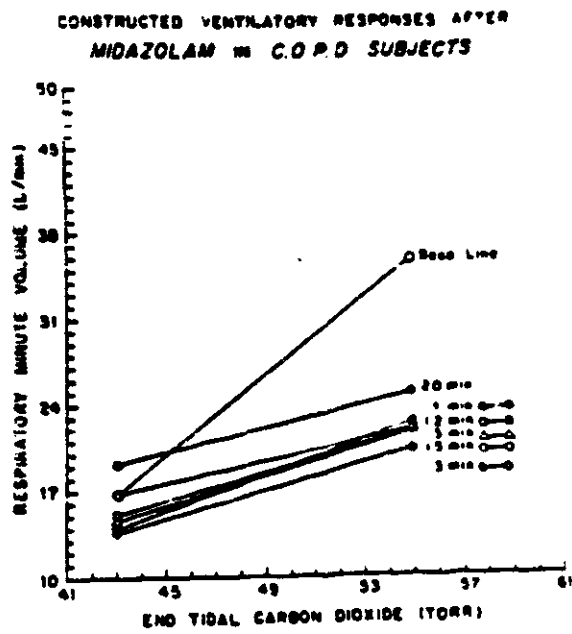
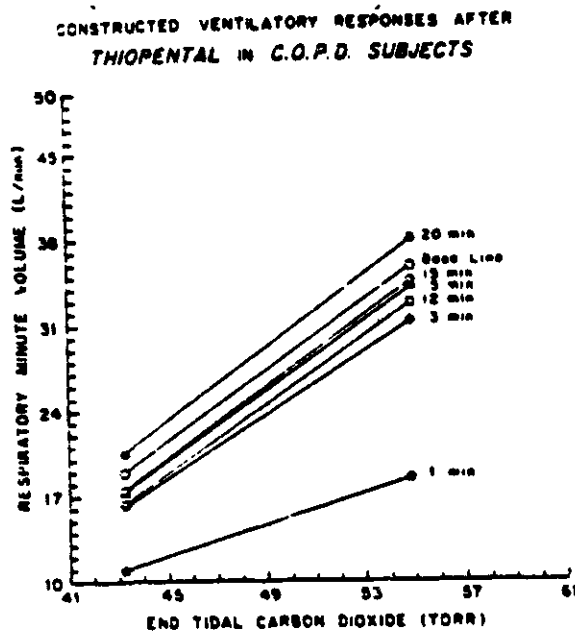
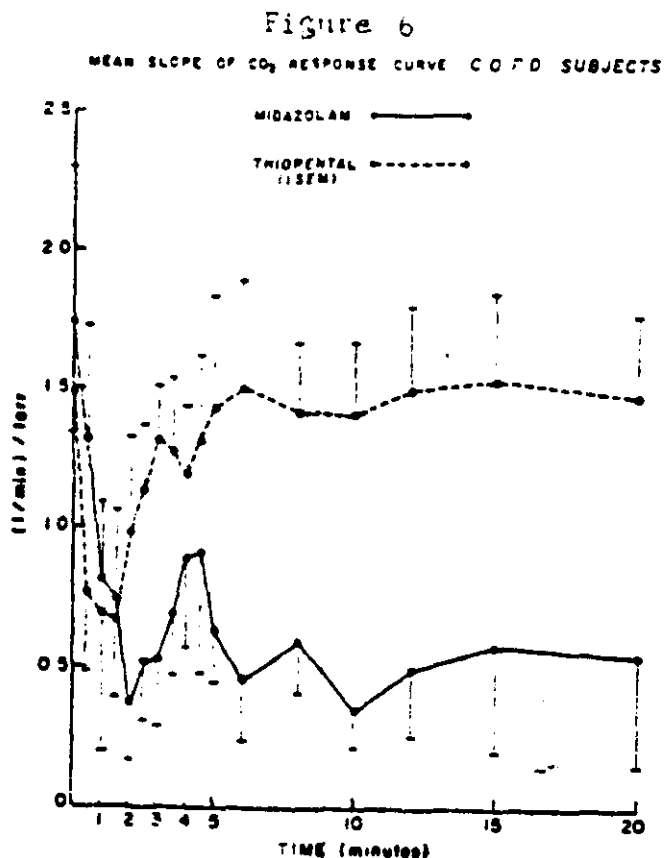


Figure - 5b



COPD SUBJECTS, MIDAZOLAM VS THIOPIENTAL (CONTINUED)



STATE OF CONSCIOUSNESS (MAXIMAL EFFECT) :

TABLE - 2
MAXIMUM PHARMACOLOGICAL EFFECT:
SCALE OF PHARMACOLOGICAL EFFECT

- 1 = NO DROWSINESS
- 2 = DROWSY, BUT RESPONDS TO COMMANDS
- 3 = ASLEEP, BUT RESPONDS TO COMMANDS
- 4 = ASLEEP, NO RESPONSE TO COMMANDS, LID REFLEX PRESENT
- 5 = ASLEEP, NO RESPONSE TO COMMANDS, LID REFLEX ABSENT

PHARMACOLOGICAL EFFECT READINGS COMBINED FOR TWO LEVELS OF P_{CO₂} PER SUBJECT (TREATMENTS)

DISTRIBUTION OF SUBJECTS WITH RESPECT TO MAXIMUM PHARMACOLOGICAL EFFECT REACHED (A)

NORMAL SUBJECTS

PHARMACOLOGICAL EFFECT		1	2	3	4	5
# Treatments						
MIDAZOLAM	16	-	-	8	-	8
THIOPIENTAL**	16	-	-	-	-	16
DIAZEPAM	16	-	4	5	2	5

COPD SUBJECTS

PHARMACOLOGICAL EFFECT		1	2	3	4	5
# Treatments						
MIDAZOLAM	12	-	1	3	4	4
THIOPIENTAL*	12	-	-	-	3	9

(A) Statistical significance (2 x 5 analogue to Fisher's Exact Test) of paired comparison with midazolam: *P<.05, **P<.01

RECEIVED

TIMING OF PHARMACOLOGICAL EFFECT: ~~Estimated~~ Time to maximal pharmacological effect (table 2) was recorded. An attempt was also made to record the time required for subjects to return to the awake and not drowsy state. Keep in mind that data were gathered in an intense way for only 15 minutes in Part I, 30 minutes in part II and 20 minutes in part III. The data for thiopental may be more precise because these subjects tended to λ within the study period of 15 minutes (mean time to "no drowsiness" at any rate):

TABLE - 3

TIME TO REACH MAXIMUM PHARMACOLOGICAL EFFECT AND TIME TO RETURN TO AWAKE (NO DROWSINESS)
COMPARISON BETWEEN TREATMENTS (A)

	NUMBER OF TREATMENTS (2 LEVELS OF P _{ET} CO ₂)	MEAN TIME TO REACH MAXIMUM PHARM. EFFECT (in minutes)	MEAN TIME TO RETURN TO "NO DROWSINESS" (in minutes)
<u>NORMAL SUBJECTS (N=8)</u>			
MIDAZOLAM	16	2.67	123.59
THIOPENTAL	16	1.71**	14.78**
DIAZEPAM	16	4.90	94.44
<u>C.O.P.D. SUBJECTS (N=6)</u>			
MIDAZOLAM	12	3.09	72.68
THIOPENTAL	12	1.30**	23.57**

(A) Results of Analysis of Variance using the natural logarithms of the times; F-test for P_{ET} CO₂ levels was not significant for either normal or COPD subjects.

Statistical significance (two sided t-test of comparisons with midazolam) **P<.05

§ Estimation only, see text.

SAFETY:

Apnea, resolving spontaneously, was reported for one normal subject after receiving midazolam under high PCO₂ testing conditions (the investigators were prepared to manage all cases as for general anesthesia, but this was not apparently necessary).

Pain on injection was reported in one subject only, in conjunction with both injections of midazolam maleate.

Hiccoughs was reported for one normal subject following both injections of midazolam maleate. The case reports note onset about 1 minute after injection, lasting only a few minutes and mild in severity.

Most subjects manifested no change in vital signs greater than 20% during testing and none manifested severe changes (greater than 50% or required treatment).

Followup resulted in 4 cases of phlebitis being reported, all 4 λ subjects having received diazepam. This was not reported in conjunction with midazolam or thiopental. The summary does not describe these cases in more detail.

REVIEWER'S COMMENTS:

I earlier summarized 2325A (Dr. Smith's later study of IM midazolam, after he moved to Chicago). The volunteers who participated in that study received 0.07 mg/kg midazolam IM. None were over sedated afterwards. No clinically significant respiratory depression was seen. Minimal slope was 3 L/minute/mmHg. The well known respiratory depressant effect of morphine (here 0.14 mg/kg IM) was not enhanced by this dose of midazolam. This would suggest that IM midazolam can be administered for premedication on the ward (ward personnel, however good, are not as well trained to manage ventilatory emergencies as are anesthesia and recovery room personnel).

In this study (2138), let us first consider the healthy volunteers. They were administered 0.2 mg/kg IM midazolam. Half of the subjects fell asleep, lost lid reflex and did not respond to commands. Ventilatory response to carbon dioxide was still mildly subdued at the end of the 20 minute test period. In contrast, the ventilatory response to carbon dioxide had returned to 84% of control 3 minutes after the intravenous administration of 3.5 mg/kg thiopental. Diazepam also diminished the ventilatory response to carbon dioxide, although the peak slope depression was 1.19 L/minute/mmHg; ventilatory response was still mildly subdued at the end of the test period (30 minutes for diazepam). only

To err on the side of safety, I would recommend that those administering intravenous midazolam have equipment and personnel available ~~to manage~~ midazolam alone to manage underventilation and/or apnea, should it occur. In addition, the need for other anesthetic agents cannot always be predicted in full, and these may also produce underventilation and/or apnea. By the end of anesthesia and surgery ~~should no longer pose a problem, but a decision~~ ventilator has to be made that the patient's condition now justifies entrusting care to the recovery room personnel and later the ward personnel. All of this is really just standard anesthetic practice and care.

Subjects with chronic obstructive pulmonary disease (COPD) seem more sensitive to the respiratory depressant effect of midazolam intravenous. This could be because COPD patients are often more resistant to the ventilatory effect of carbon dioxide and/or because these volunteers were older than the healthy volunteers.

Joseph Gerald Reves, M.D., Univ. of Alabama, Birmingham.
Study No. 1092 (see also Study No. 1092A, previously summarized)

This was an open study in patients with ischemic heart disease scheduled for myocardial revascularization surgery. There were a number of kinks in this study, making it seem sort of like a rehearsal for study # 1092A; in addition, the sponsor's summary does not include the neat sort of graphs that made study # 1092A easier to follow.

Ten patients received induction of general anesthesia with midazolam ^{maleate} and ten with diazepam. ~~[Premedication was to consist of diazepam 0.7-0.15 mg/kg orally, morphine 0.1 mg/kg IM and scopolamine 6-8 ug/kg IM---all administered one hour before surgery; in actual practice diazepam was administered irregularly (only 3/10 midazolam patients received diazepam premedication), the dose range of scopolamine was greater than planned (2-9 ug/kg) and only morphine appeared consistent (although one patient in the midazolam group did receive 0.15 mg/kg); the time before induction turned out to be 105-300 minutes, instead of the planned 60 minutes (mean 202 minutes for midazolam and 152 minutes for diazepam induction),~~ inductio
The most important differences have to do with oxygen delivery: Control measurements differed in that the diazepam group was breathing room air and the midazolam group was breathing 100% oxygen ---and--- During the 1-2 minutes post induction, diazepam patients breathed 50% oxygen (and presumably 50% nitrous oxide; the summary is not clear on this point and I cannot figure out more with a reasonable search of the case reports) and midazolam patients breathed 100% oxygen.

Invasive monitoring and data gathering was as for Study No. 1092A, previously summarized. Endotracheal intubation was also as for 1092A: pancuronium 0.1 mg/kg and also use of 4 ml of 4% lidocaine spray at the time of intubation.

All patients were male, the majority ASA Risk III. Most patients were on coronary vasodilators (isorbide &/or nitroglycerin) and 85% were chronically on propranolol (9/10 midazolam & 8/10 diazepam).

RESULTS:

The following tables, from the sponsor's summary, show the results. Please note that Table II has been revised since submission of the NDA (some of the units and abbreviations were in error---Stroke Index is in ml/m², not ml/min/m² as originally submitted, etc.). I have also rearranged the order so that, where feasible, monitored determinations appear before calculated determinations; this is not always possible because some tables (such as Table IV) include both.

TABLE III
HEMODYNAMIC PARAMETERS
PRESSURES
(N=10 patients per test drug group)

Parameter/Treatment	Control	Mean Change from Control [#]					
		(1)	(2)	(3)	(4)	(5)	(6)
MAP (mm Hg)							
Midazolam	102.0	-15.5*	-21.5*	-23.0*	- 8.0 [†]	-24.0* [†]	-25.0*
Diazepam	94.5	-11.4*		-22.6*	6.9	-11.5*	-18.9*
RAP (mm Hg)							
Midazolam	11.9	0.6	1.5	- 0.7	- 0.8	- 0.7	- 0.5
Diazepam	9.4	0.8		- 0.1	- 0.4	- 1.3	- 1.6*
MPAP (mm Hg)							
Midazolam	27.0	- 1.5	- 2.9	- 5.1*	- 2.9	- 5.9*	- 5.9*
Diazepam	21.9	- 0.9		- 2.9*	0.6	- 2.3	- 3.9*
MPCMP (mm Hg)							
Midazolam	17.9	- 1.0	- 2.6	- 4.5*	- 3.9* [†]	- 5.4*	- 4.5*
Diazepam	13.4	- 0.5		- 1.6	1.3	- 2.8	- 2.8*

- #(1) = 1-2 minutes after induction
 (2) = 4-5 minutes after induction (midazolam group only)
 (3) = 3-4 minutes after pancuronium
 (4) = 1-2 minutes after intubation
 (5) = 4-5 minutes after intubation
 (6) = 9-10 minutes after intubation

*Significant change from control ($P < 0.05$, 2-sided test)

[†]Significantly greater change from control with midazolam compared with diazepam ($P < 0.05$, 2 sided-test)

TABLE IV
HEMODYNAMIC PARAMETERS
HEART RATE AND INDICES
(N=10 patients per test drug group)

Parameter/Treatment	Control	Mean Change from Control [#]					
		(1)	(2)	(3)	(4)	(5)	(6)
HR (beats/min)							
Midazolam	54.8	11.2* [†]	9.2*	16.0* [†]	23.6*	21.6*	20.0*
Diazepam	69.6	- 1.4		6.3	21.4*	11.7*	10.1*
RPP (beats mm Hg/min)							
Midazolam	8.3	0.30	- 0.71	- 0.10	2.19*	0.15	- 0.27
Diazepam	9.4	- 1.33*		- 2.02*	3.01*	- 0.21	- 1.42*
SVRI (dynes-sec-cm⁻⁵/m²)							
Midazolam	923.5	-238.8*	-234.5*	-335.1*	-208.9* [†]	-283.5*	-245.5*
Diazepam	781.2	-40.4		-187.4*	40.7	-79.1	-107.2
PVRI (dynes-sec-cm⁻⁵/m²)							
Midazolam	82.7	- 3.2	0.1	- 9.5	1.8	0.2	- 6.1
Diazepam	72.3	17.9		- 7.2	7.1	7.1	- 0.1

- #(1) = 1-2 minutes after induction
 (2) = 4-5 minutes after induction (midazolam group only)
 (3) = 3-4 minutes after pancuronium
 (4) = 1-2 minutes after intubation
 (5) = 4-5 minutes after intubation
 (6) = 9-10 minutes after intubation

*Significant change from control ($P < 0.05$, 2-sided test)

[†]Significantly greater change from control with midazolam compared with diazepam ($P < 0.05$, 2 sided-test)

J.G.Reves, Birmingham, Study No. 1092, page three of Clinical Summary
 This table was revised by ROCHE on or about 8 May 1984, at the request of
 the Medical Officer, and this was done for correction of units of measurement.

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TABLE 11
 HEMODYNAMIC PARAMETERS
 CARDIAC FUNCTION
 (N=10 patients per test drug group)

Parameter/Treatment	Control	Mean Change from Control [†]					
		(1)	(2)	(3)	(4)	(5)	(6)
CI (L/min/m²)							
Midazolam	2.4	- 0.02	- 0.16	0.14	0.19	- 0.12	- 0.22
Diazepam	2.3	- 0.26		- 0.13	- 0.01	- 0.10	- 0.24
SI (ml/m²)							
Midazolam	43.9	- 6.2*	- 7.0*	- 7.0*	-10.0*	-13.1*†	-14.2*†
Diazepam	33.6	- 2.9		- 4.3*	- 7.9*	- 6.0*	- 7.0*
SV (ml)							
Midazolam	85.7	-13.0*	-14.7*	-14.9*	-20.2*	-26.0*†	-28.0*†
Diazepam	66.5	- 5.5		- 8.5*	-15.4*	-11.6*	-13.7*
LVSWI (g-m/m²)							
Midazolam	50.8	-14.5*	-18.3*	-17.4*	-13.8*	-23.0*†	-25.0*†
Diazepam	36.7	- 7.4*		-12.7*	- 6.2*	- 9.6*	-13.1*
RVSWI (g-m/m²)							
Midazolam	8.8	- 2.5*	- 3.6*	- 3.5*	- 2.8*	- 4.7*†	- 5.1*†
Diazepam	5.9	- 1.3*		- 1.9*	- 1.1	- 1.4*	- 2.1*

(1) = 1-2 minutes after induction
 (2) = 4-5 minutes after induction (midazolam group only)
 (3) = 3-4 minutes after pancuronium
 (4) = 1-2 minutes after intubation
 (5) = 4-5 minutes after intubation
 (6) = 9-10 minutes after intubation
 *Significant change from control (P < 0.05, 2 sided-test)
 †Significantly greater change from control with midazolam compared with diazepam (P < 0.05, 2 sided-test)

Effect on Mean Perfusion Pressure and Peripheral Resistance During Coronary Bypass (Midazolam Group Only): Mean perfusion pressure was minimally decreased from control during the first three minutes, followed by minor increases. Peripheral resistance was minimally increased from baseline for the five-minute period. None of the changes were statistically significant (Table V). These measurements were not taken in the diazepam group. Data from patients and and the five-minute data from patient were excluded from these analyses because the pump flow was not kept constant.

	Control	Mean Change from Control				
		1 min.	2 min.	3 min.	4 min.	5 min.†
Mean Perfusion Pressure	53.0	- 1.3	-3.0	- 1.5	0.1	0.4
Peripheral Resistance	1408.5	50.7	1.5	48.9	98.3	91.3

† N=7

SAFETY:

Respiratory observations were as expected for induction of anesthesia; apnea lasting 15-60 seconds was reported in 7 midazolam patients; such records were not kept for diazepam patients.

Pain on injection was reported for two midazolam patients; records were not kept for diazepam treated patients.

One midazolam treated patient manifested a severe increase (greater than 50%) in heart rate on induction of anesthesia. No patients required treatment for changes in vital signs. Information to locate the case report is not currently available to me. The case reports are superficially filled out (unlike study # 1092A) so pursuit of this matter does not seem worthwhile.

REVIEWER'S COMMENTS:

As noted before, this study seems like a rehearsal for Study # 1092A. Anyway, it took this study to get the kinks out. I checked a few of the case reports; timing is often missing.

Much precise information is omitted in favor of some mark to note that an event took place, etc.

The information about midazolam should be considered alone because there is sufficient difference in methodology between groups to preclude comparison. Especially important is the fact that oxygen delivery varied between groups; the role of nitrous oxide cannot be determined from a reasonable search of the case report forms.

J.G.Reves, Study 1092, page 5ive of clinical summary-----

From all of this we see that mean arterial pressure fell moderately after induction with midazolam maleate and that the heart rate rose slightly. The net result was that rate-pressure product remained about the same and left ventricular stroke work index fell moderately.

Pulse rate rose moderately after administration of pancuronium but mean arterial pressure did not change. Endotracheal intubation was associated with additional acceleration of heart rate and a return of mean arterial pressure to near control level; this is not surprising since anesthesia was very light. It is only for the measurements made 1-2 minutes after intubation that rate-pressure product was significantly above control level; at that time left ventricular stroke work index was still below control. It appears that the only hint of unfavorable oxygen demand versus supply ratio had to do with endotracheal intubation under light general anesthesia. Even then, this was less than that seen in some of the other studies under ~~light~~ light general anesthesia. The reasons for this probably have something to do with chronic propranolol medication in the majority of patients and with ~~the~~ premedication possibly ~~enhancing~~ enhancing the depth of anesthesia. In any event, the mean heart rate was slow to begin with (55/minute) and never rose above 78/minute.

Dr. Reves is generally recognized by his peers as being an authority of cardiovascular anesthesia, especially anesthesia for myocardial revascularization. He seems to have entrusted most of this study to a Dr. Samuelson (most case reports are signed: "Reves/Samuelson").

Protocol # 2152A, Michael Melvin, M.D., Univ. of Calif., San Francisco, Dept. of Anes.

This was an open special study designed to determine the effect of midazolam maleate on the minimum alveolar concentration (MAC) of halothane. Fifty one ASA Status I & II patients, aged 29-55 years, consented to participate in this study. Patients were assigned to receive one of four doses of midazolam for induction of anesthesia and they were unpremedicated: 0.15 mg/kg (n = 13), 0.30 mg/kg (n = 12), 0.45 mg/kg (n = 14) & 0.6 mg/kg (n = 12). The rate of administration through a free running intravenous line was 0.075 mg/kg approximately every minute. Halothane was administered immediately after loss of response to commands, loss of eyelid reflex and loss of voluntary movement in 37/51 cases, with a mean dose of 0.21 mg/kg midazolam; halothane completed the induction of anesthesia in the remaining cases (this was not really a precise study of induction of anesthesia, interest being centered on dose response of midazolam for decreasing MAC). When a sufficient depth of anesthesia was achieved, the patients were intubated. End tidal halothane concentration was then brought to a predetermined level, starting with 0.6% for the first patient and working in increments of 0.1%, up or down, in subsequent patients as dictated. At equilibrium, surgical incision was performed and the patient was observed for movement. No other drugs were administered until after surgical incision (the halothane was in oxygen). After the surgical incision, all patients received nitrous oxide in oxygen for maintenance, along with the halothane, and any other indicated additional drugs (such as narcotics and muscle relaxants).

MAC or minimal alveolar concentration is the end tidal concentration of volatile liquid inhalational agent which will inhibit patient response to surgical incision in 50% of patients so exposed. Thus the main purpose of the study was finished in each case with the surgical incision and any other indicated drugs could be added. Inspired halothane concentration is greater than end tidal concentration, by no set amount but somewhere in the neighborhood of 150%. The MAC concept was developed at the Univ. of Calif., San Francisco, by E.I. Eger, II, et. al.

Serial midazolam samples were taken for pharmacokinetic study, but as it turned out this was only feasible in 17 patients. I got nothing out of the results as reported and will defer useful deductions, if any, to the Division of Biopharmaceutics, which has been consulted by HFN-160. No more will be said about this in the clinical review of this study.

RESULTS:

For the record, the following inductions were completed with midazolam alone: 0.15 mg/kg--6/13, 0.30 mg/kg--11/12, 0.45 mg/kg--10/14, 0.60 mg/kg--10/12. The remaining inductions were completed with halothane. Mean induction dose in those cases completed with midazolam was 0.21 mg/kg (median 0.23 mg/kg). Because of use of halothane, when inducted, time to induction did not vary greatly with dose of midazolam (mean time 144 seconds, range 90-240 seconds, median time 150 seconds). None of this should alter the results of the main purpose of the study, to determine MAC.

Time from initial injection of midazolam to surgical incision was as follows: 0.15 mg/kg--mean 44 min., median 44 min, range 30-64 min., 0.30 mg/kg--mean 38.5, median 37, range 27-58, 0.45 mg/kg--mean 38, median 38, range 24-60, 0.60 mg/kg--mean 50, median 43.5, range 32-85.

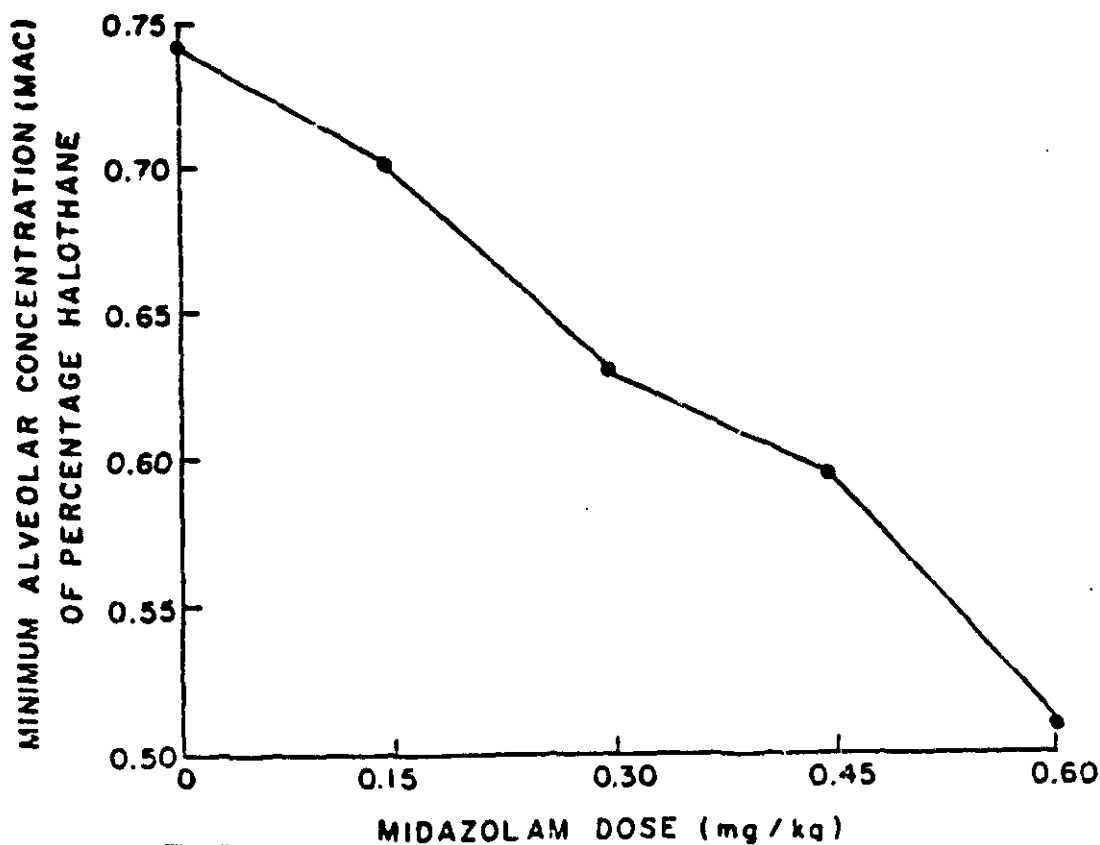
The next page of this review is really the sixth page of the sponsor's summary in 1.33 of the NDA. The table (Table III) and the figure (Figure 1) show that MAC halothane diminished in relation to the dose of midazolam maleate used for induction of general anesthesia:

TABLE III
END-TIDAL CONCENTRATION OF HALOTHANE

Midazolam Dose Level (mg/kg)	End-Tidal Concentration Halothane (%)	No. Patients	No. Patients with Successful Response	Probability of Successful Response	MAC ± 1 S.E.††
0.15	0.6	4	0	.00	.700 ± .015
	0.7	6	3	.50	
	0.8	3	3	1.00	
		13			
0.30	0.5	2	0	.00	.629 ± .035
	0.6	5	2	.40	
	0.7	4	3	.75	
	0.8	1	1	1.00	
		12			
0.45	0.4	1	0	.00	.594 ± .037
	0.5	3	1	.33	
	0.6	6	2	.33	
	0.7	4	4	1.00	
		14			
0.60	0.4	3	0	.00	.509 ± .039
	0.5	5	3	.60	
	0.6	3	2	.67	
	0.7	1	1	1.00	
		12			

†successful response is defined as no movement during surgical incision.
 ††S.E. = standard error of estimate

Figure 1
ESTIMATED MINIMUM ALVEOLAR CONCENTRATION (MAC) OF HALOTHANE FOR EACH MIDAZOLAM TREATMENT LEVEL



Protocol No. 2152A, page 3hree of clinical review---

SAFETY:

Adverse observations during induction of anesthesia were about as expected for induction of general anesthesia. One patient was listed as having a "severe" increase in pulse rate during induction. An examination of the case report reveals that initial pulse rate was 70/min. and that maximum rate during or shortly after induction was 110/minute, no big deal. This lasted three minutes and did not require treatment. The investigator felt that this was "possibly" related to test drug administration (intermediate between "probable" and "remote"). Pulse also increased "severely" for 25 minutes during maintenance; this did not require treatment and was rated "remote" as far as relationship to test drug administration. I am afraid that none of this is very informative but there seems to be no justifiable reason for additional pursuit, especially since the highest heart rate noted was 110 per minute.

One adverse experience is listed as "chest pain", judged "remotely" related to test drug administration. I thought that I had better check; with the help of Karen Church of ROCHE, I determined that this was patient . The case report notes that she was about 55 years of age in 1980, the year of surgery. She had a history of myocardial infarction in 1967 (!), without recurrent cardiac symptoms. Anesthesia and surgery (right total hip arthroplasty for rheumatoid arthritis) was on 13 March 1980. Moderate hypotension developed in the recovery room, lasting 15 minutes and responding to fluid and blood, judged "remotely" related to test drug administration. Mild chest pain developed on 19 March 1980, or 6 days later; duration is not available but it ended the same day. This was judged "remotely" related to test drug administration; at last followup, the patient was checked as "still under treatment" (the alternatives being the same as on Form FD 1639). It is the opinion of this reviewer that there is no reasonable association between the development of chest pain on the sixth postoperative day and the administration of test drug.

Robert Fragen, M.D., Northwestern. Study No. 2027A:

This was a special study of intraocular pressure:

Thirty unpremedicated ASA Risk I & II patients scheduled for non-ophthalmological surgery under general anesthesia with endotracheal intubation participated in this study. All patients with increased intraocular pressure were excluded. They were randomly assigned to three groups for induction of anesthesia: 1. 0.15-0.32 mg/kg midazolam maleate, 2. diazepam 0.3-0.4 mg/kg, 3. thiopental 4 mg/kg. In addition, diazepam inductions requiring more than 0.4 mg/kg were completed with thiopental. The topical anesthetic, proparacaine, was administered to the eye before-before baseline intraocular pressure measurement (calibrated Perkins applanation tonometer). This was repeated 1 and 3 minutes post induction. Succinylcholine 1 mg/kg was then administered to facilitate intubation. Another intraocular pressure determination was performed 1 minute post succinylcholine. The last determination was 1 minute post intubation. ↑

Assignment was randomized. Drug usage was known to the principal investigator but not to the ophthalmologist performing the intraocular pressure measurements.

RESULTS:

Intraocular pressure fell following induction with all agents. None of the agents afforded protection against the intraocular pressure rise associated with administration of succinylcholine or endotracheal intubation.

SAFETY: There were no real safety problems. Blood pressure and pulse tended to rise after succinylcholine administration and after intubation.

One midazolam patient had the intravenous catheter in place for 38 hours and then developed phlebitis, lasting 4 days. This does not seem reasonably associated with test drug administration.

Redness and tenderness was noted on days 1 & 2 in one thiopental patient. Burning on injection with pain was noted ~~during injection of diazepam~~ in three patients who received diazepam.

The second page of this summary is the intraocular pressure table that appears on page 171 of NDA 18-654, Volume 1.14.

The patients were ventilated with oxygen until after intubation and then choice of anesthesia was left up to the anesthetist, the study having been judged terminated for that patient.

TABLE 2

Intraocular Pressure (Torr Mean ± S.D.)
(Overall)

<u>Drug</u>	<u>Control</u>	<u>1 Minute Post Induction</u>	<u>3 Minutes Post Induction</u>	<u>1 Minute Post Succinylcholine</u>	<u>1 Minute Post Intubation</u>
Midazolam maleate	16.3±3.16	11.8±2.70***	9.6±3.30***	21.6±3.31***	24.9±5.93***
Thiopental	17.8±4.47	13.4±4.50***	12.4±5.32***	23.7±7.38**	26.9±8.31***
Diazepam (N=10†)	17.4±2.59	12.1±2.23***	11.5±1.96***	23.7±4.76***	27.1±5.55***
Diazepam alone (N=5††)	18.0±2.35	11.4±1.34*	10.8±1.92**	22.6±5.68*	25.0±5.70
Diazepam+Thiopental (N=5†††)	16.8±2.95	12.8±2.86*	12.2±1.92**	24.8±3.96**	29.2±5.07**

*p<0.05 from control

**p<0.01 from control

***p<0.001 from control

†Includes all the patients in the diazepam group

††Includes only the patients who received diazepam alone

†††Includes only the patients who received diazepam and also thiopental

Protocol 2188A

James E. Cottrell, M.D. & Wm. A. Shucart, M.D., Anesthesiology, State Univ. of New York, Brooklyn Downstate Medical Center

This is a study of the effects of midazolam hydrochloride versus thiopental sodium for induction of general anesthesia in neurosurgical patients with intracranial mass, a normal intracranial pressure (less than 19 mmHg) and impaired cerebral compliance. Assignment was randomized, double-blind (third party open) and parallel groups were employed. At the time of submission of the NDA, the study was just starting good, with 10 patients participating (6 midazolam & 4 thiopental); only trends can be demonstrated at this time, so this review will be shortened.

Patients were chosen who, for other reasons, would benefit ^{from} the insertion of a subarachnoid screw in the cranial area prior to surgery, for the monitoring of intracranial pressure. First, it was determined that intracranial pressure was in the physiologic range. Then, 1 ml of saline was injected to confirm the impression of decreased compliance (a two to four mmHg or greater increase in intracranial pressure). Immediately after intracranial pressure returned to normal, following the saline injection, induction was started in these unpremedicated patients with 0.25 mg/kg midazolam or 4.0 mg/kg thiopental over 30 seconds; increments of 25% were used 2 minutes later to complete induction, if needed. In practice, the mean induction dose of midazolam totaled 0.279 mg/kg, no increments were required in two cases and one increment was required in six cases; the mean induction time (no response to command, loss of eyelid reflex & loss of skeletal muscle movement in response to placement of anesthesia mask) was 131 seconds. The mean dose in thiopental patients was 4.202 mg/kg, no increments were required in three cases and one increment was required in one case; the mean induction time was 65 seconds. The person administering test drug knew which drug was administered but the person monitoring the patient (including intracranial pressure) was not aware of the identity of test drug. I could find no information (protocol, summary of results or spot check of case reports) about inhalational anesthetics or other gas delivery during induction and the gathering of data.

One minute after induction of anesthesia was judged complete, pancuronium was administered to provide skeletal muscle paralysis for endotracheal intubation. I cannot find information about the dosage of pancuronium employed, other than the fact that it was an intubating dose; this information is not usually available on the case reports, either, but in one of the cases which I checked the dose of pancuronium was 2 mg plus 2 mg, total 4 mg, listed under "COMMENTS, if any."

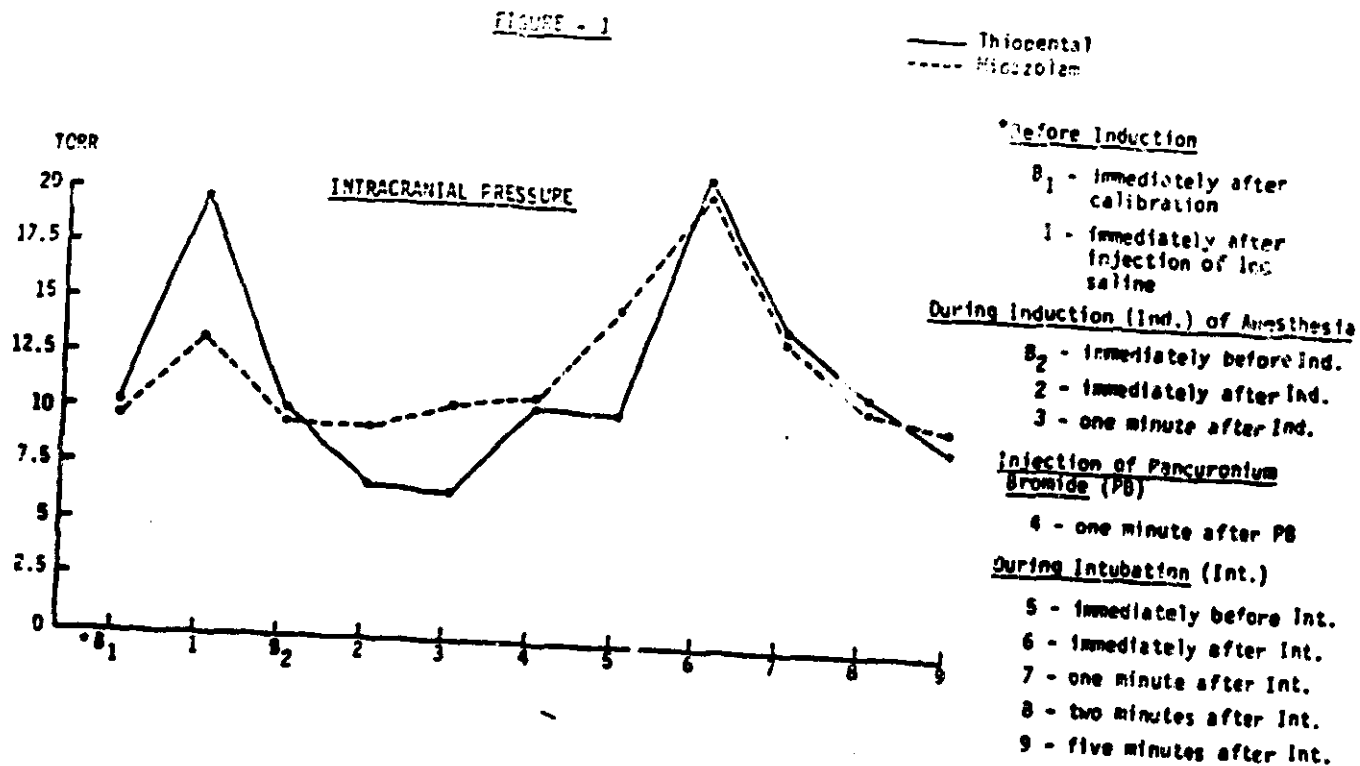
Upon completion of neuromuscular blockade, 50% of the total induction dose of midazolam or thiopental was administered in preparation for endotracheal intubation. Intubation was performed 3 1/2 minutes after this dose of midazolam or one minute after this dose of thiopental.

Vital signs were measured serially, as was intracranial pressure. Mean arterial pressure was calculated as = diastolic plus 1/3 of pulse pressure.

One patient _____ unexpectedly manifested a baseline intracranial pressure of 23 mmHg and was replaced in the study by patient _____

RESULTS:

The figure on the top of the next page is from the sponsor's summary and it shows most of what can be learned from these preliminary data. Midazolam lowers intracranial pressure slightly, as do most other induction agents (exception, ketamine). Midazolam may afford some protection against elevation in intracranial pressure due to the trauma of endotracheal intubation; in any case, the rise at that point in time reached a mean of only 20 mmHg.



Let's defer judgement about circulatory changes based upon this preliminary data. Midazolam use was not accompanied by significant pulse rate change in these 6 patients, nor was much change noted after the administration of pancuronium, but midazolam afforded no protection against heart rate rise associated with the trauma of endotracheal intubation (baseline 75/min.---105/min. immediately after intubation, then subsiding slightly). Mean arterial pressure also rose immediately after intubation (baseline 95 mmHg---135 mmHg immediately after intubation, then returning to baseline over the next two minutes); the administration of midazolam was accompanied by a drop in mean arterial pressure from 95 mmHg baseline to 87 mmHg or so which persisted through pancuronium administration and did not rise until intubation.

SAFETY:

There were two deaths in the midazolam group and both were late developing complications:

An autopsy was not done.

Patient 65 y. m. with tumor of right cerebral hemisphere. Surgery was on 20 NOV '81. There were no remarkable perioperative findings. On the eighth postoperative day the patient went into cardiopulmonary collapse, judged due to pulmonary embolism. Afterwards, the clinical impression was that the arrest led to brain death. The patient died on the 23rd postoperative day. The investigator has the opinion that these adverse experiences are remotely related to the administration of midazolam ("Remote" being the lowest possible classification of drug relationship listed on the case report form check list).

Patient This case is reconstructed from: 1. Case report (superficial), 2. Adverse experience (Form 1539) Volume 1.139, pages 2-4, 3. Vol. 1.34, pages 92 & 104, 4. Telephone conversations with Karen Church of ROCHE on 9 & 10 May 1984. Definitive evaluation was delayed because the investigator did not notify ROCHE; this complication was discovered from the little bit of information on the case report form. Once discovered, ROCHE borrowed the hospital record and established beyond a reasonable doubt that there was no reasonable association between this adverse experience and use of midazolam as a test drug; the staff member in charge no longer works for ROCHE and the hospital record was returned without copying. Later, the investigator sent a letter to ROCHE at their request; he tells much the same story but the letter seems to contain proofreading errors or non-superimposable dates.

Diagnosis on the case report form is listed simply as "Brain Tumor" and the date of Craniotomy is listed as 9 October 1981. On 10 October 1981, the patient became comatose; a C-T Scan was compatible with right lateral ventricular bleeding. Surgery was performed to relieve this condition but the surgery did not result in any improvement in state of consciousness. The patient had a steady downhill course to death on 17 October 1981. No autopsy was performed. The record lists cardiopulmonary arrest secondary to cerebral edema as the main cause of death. The cerebral edema was judged due to "brain tumor".

I am not pleased with the indifferent handling of the report for case 6, and perhaps case 8, by the investigator, creating more work for ROCHE and for me. I now feel that there is no reasonable association between the administration of midazolam and these two fatal adverse experiences. For purposes of this application no action appears indicated, however, the Division of Scientific Investigation should at least be alerted to the relatively superficial reporting of fatal adverse experiences by this investigator.

REVIEWER'S COMMENTS:

This ongoing study suggests that midazolam behaves in a manner typical for induction agents other than ketamine, lowering intracranial pressure slightly to moderately. The circulatory data appears too preliminary to make meaningful comments.

There appear to be no serious complications reasonable associated with the administration of midazolam. The two fatal adverse experiences cited above are for the record only and do not appear related to the administration of midazolam. Scientific Investigations has been notified (.. Chernov--10 May 1984) of superficial reporting of surgical complications by this investigator.

N-18654-7

Study No. 1083, Carter M. Ballinger, M.D., Dept. of Anes., New Jersey Medical School, Newark.

This was a special cerebrospinal fluid pressure study, conducted in thirteen ASA Risk I & II patients scheduled for elective abdominal or lower extremity surgery under spinal anesthesia. They consented to the extra cerebrospinal fluid pressure testing needed during the 15 minutes of data gathering. Lumbar puncture was performed with a 22 gauge needle and a manometer calibrated in mmH₂O took baseline measurement. A single intravenous dose of either midazolam maleate 150 ug/kg (not to exceed 1.25 mg/15 seconds) or thiopental 3000 ug/kg (not to exceed 25 mg/15 seconds) was administered; assignment was randomized. The cerebrospinal fluid pressure measurement was repeated every minute for 15 minutes or almost to 15 minutes. Patients were unpremedicated.

Thirteen patients participated but technical difficulties precluded the generation of definitive data in all but 8 patients, 4 per group. There were apparently no ventilatory problems to preclude testing (patients were in the lateral decubitus position during testing). The spinal anesthetic was administered through the lumbar puncture site after the 15 minutes of testing. The summary does not mention the spinal anesthetic used.

RESULTS:

Patients manifested moderately decreased cerebrospinal fluid pressure, compared to baseline, throughout the test period for both drugs. This is best seen from TABLE II, reproduced below (Volume 1.14, page 126 of sponsor's summary) and Figure 1, reproduced on the next page (page 127 of IBID):

TABLE II

Cerebrospinal Fluid Pressure (mmH₂O)
(Midazolam Maleate Group)

Pt. No	Baseline	MINUTES POST INJECTION															
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	130	164	164	158*	-	156	160	154	152	152	152	152	152	152	170**	180	-
4	180	150*	160	160	172	170	168	150	135	120	111	110	115	120	120	-	-
9	164	150	152*	152	150	150	150	150	150	150	152	150	150	149	150	148	-
10	198	-	190*	186	178	184	184	188	190	-	-	-	-	-	-	-	-
Mean	181	155	167	164	167	163	166	161	157	141	138	137	139	140	147	164	-
+ S.D.	+14	+8	+16	+15	+15	+15	+11	+18	+23	+18	+24	+24	+21	+18	+25	+23	-

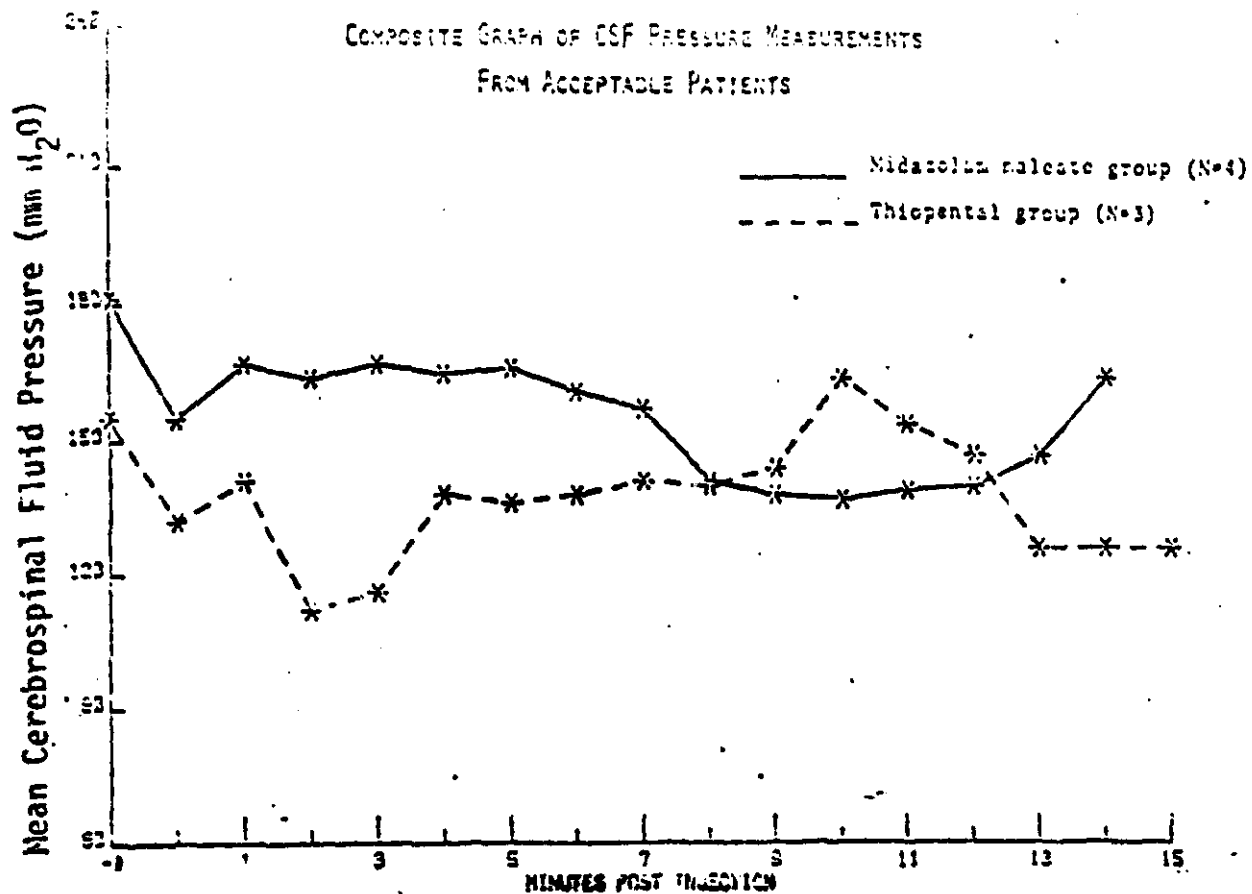
(Thiopental Group)

Pt. No.	Baseline	MINUTES POST INJECTION															
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
2	132	132*	-	80	80	124	124	136	134	136	134	200**	170	-	-	-	-
5	180	-	142	124*	135	152	156	150	160	158	162	166	166	168	-	-	-
7	152	-	140*	132	134	138	128	128	129	126	136	125	125	125	126	126	126
Mean	155	132	141	112	116	138	136	133	141	140	144	164	154	147	126	126	126
+ S.D.	+24	+0	+1	+28	+31	+14	+17	+11	+17	+16	+16	+38	+25	+30	+0	+0	+0

* Absence of eyelid reflex
** Moving

Ballinger, No. 1083, page 2wo of summary----

FIGURE 1

**SAFETY:**

There were no real safety problems that might have bearing on the package insert. Shallow respiration is reported in one midazolam subject and three thiopental subjects. Increased respiratory rate of more than 20% is reported in 4 patients after midazolam administration and 2 patients after thiopental administration. This was judged to be a compensatory mechanism (the lateral decubitus position and ventilation is not ideal for maintenance of an airway after induction of anesthesia, even though some clinicians ~~with plenty of assistance use induction agents before spinal or epidural anesthesia, especially spinal anesthesia~~ are able to use intravenous induction agents before spinal or epidural anesthetic administration; they usually have plenty of assistance).

There were no reactions at the injection site.

Protocol 2210A

Richard Wright, M.D. & John A. Reitan, M.D., Univ. of Calif., Davis

This was a study of midazolam versus diazepam for induction in 50 ASA Status III patients. At the time of submission of the NDA, one patient has participated in the study; obviously, no conclusions about dosage can be reached on the basis of one case.

SAFETY: The one patient incurred a myocardial infraction. Historically, this was entered on the case report form and picked up by ROCHE. They requested additional details and the investigator was slow about providing the details. I notified the Office of Scientific Investigation (H. Chernov) because they were looking for centers to investigate anyway; I thought that there was cause for this investigator to be investigated by means other than chance. When the investigator found out selection. about the upcoming investigation, he provided additional details to ROCHE and these were submitted by ROCHE to the Clinical Investigations Branch, Division of Scientific Investigations, on 13 July 1982.

The patient was a female, born in 1917, who incurred surgery on 11 August 1981. Preoperative diagnosis was Peptic Ulcer Disease and the operation performed was Vagotomy and Pyloroplasty. She was judged ASA Status III because of severe chronic obstructive pulmonary disease, coronary artery disease and peripheral vascular disease (from case report form). Chronic medications included: Cholel 200 mg every 6 hours, tetracycline 250 mg every 6 hours, cimetidine 300 mg every 6 hours, propranolol 40 mg twice daily and Riopan 30 ml after meals. Premedication consisted of morphine 9 mg IM and glycopyrrolate 0.2 mg IM.

Blood pressure before administration of study drug was 133/65, heart rate 91/minute. Blood pressure during induction was 123/63, heart rate 97/minute. The dose of test drug (midazolam) administered was 0.147 mg/kg over 1.5 minutes (Weight: 61 kg). About 75 seconds after induction was completed, the blood pressure fell to 101/58 (heart rate 94/minute). This was treated with 50 ug phenylephrine intravenously. The blood pressure recorded one minute later was 123/65 (heart rate 97/minute).

Forty five seconds after phenylephrine administration, fentanyl (dose not stated) was administered intravenously and nitrous oxide was started. Propranolol was also administered during anesthesia, but timing and dosage is not clear from the case report form.

About 25 minutes after phenylephrine administration, blood pressure rose to 195/85 (heart rate 88/m). This was managed with addition of halothane 1.5% and the blood pressure slowly fell, reaching 126/69 about one hour later. Ten minutes later, blood pressure was again high (180/100, heart rate 94/m) and halothane 1.5% was "turned up". The last recorded pressure was 170/90, another 30 minutes later, and the pulse at that time was 107/m; halothane was turned off. Anesthesia ended 20 minutes later. To allay confusion about timing: induction was complete at 08 hours, 2 minutes and 45 seconds and is recorded as having ended at 10:50 hours. Estimated blood loss was 110 ml.

^{anesthesia}
and after induction

Incidentally: Blood gases preoperatively leave this reviewer confused as to the preoperative diagnosis of chronic obstructive pulmonary disease. PaCO₂ was 39 preoperatively on spontaneous ventilation and was 33 immediately after induction. PaO₂ at these respective times were 268 & 208, the first with FiO₂ 1.0 (100% oxygen?) and the second with FiO₂ 0.5. Base excess was a negative -6 & -7, but pH was 7.34 & 7.36.

In the recovery room, the patient noted chest pain radiating to the jaw. ST segment changes were noted on ECG. She went from the recovery room to the coronary care unit,

where the development of Q-wave in V3 and enzyme changes led to a diagnosis of myocardial infarction. Location was judged to be anteroseptal subendocardial. She remained on the coronary care unit for seven days. According to a letter from Dr. Reitan to ROCHE, dated 29 June 1982, she was then discharged back to the surgical floor. She was then discharged, apparently recovered from surgery and with no additional coronary artery problems. "She has been seen at followup clinic without untoward cardiac problems."

Dr. Reitan also states that no ST segment changes were noted on ECG during induction of anesthesia. These were first noted late in the case and became more pronounced in the recovery room. (If this review is re-typed, this paragraph goes before the last one).

The investigator also renders the opinion that this unfortunate myocardial infarction cannot be attributed in any way to the anesthetic induction agent. He cites a rather stressful surgical procedure, hypertension and hypotension, "It is my opinion that this patient developed her problems secondary to the surgery and maintenance of anesthesia and not to the agents used in inducing the anesthesia initially."

REVIEWER'S IMPRESSION: Anesthetics are not administered alone. In this case we must add a list of chronic medications to the drugs used to manage anesthesia. I can't determine for sure whether or not this patient was hypertensive, but if so it was an intermittent or labile hypertension; the first blood-pressure recorded was while the patient was awaiting induction of anesthesia (133/65). If I had one drug that I wish had not been administered, it would be phenylephrine. ~~It is not clear what parenteral fluids might have been administered first, if any.~~ This is pure second guessing, because I was not present and do not understand fully from the case report what else was done (particularly use of large volume parenterals).

I would make no judgement against any use of midazolam based on this case report alone and I would judge that midazolam was not a deciding factor in the development of myocardial infarction. ~~midazolam's contribution to this adverse experience; if any, appears to be at worst~~ *but that it must be considered part of the overall picture.*

It is regrettable that the investigator team was not more prompt and thorough in reporting this adverse experience. Maybe we would know more.

Main Source Used: 13 July 1982 Submission, Dr. to H. Chernov, Clinical Investigations Branch of Div. Scientific Investigations (also then known as HFD-180).

SERIOUS ADVERSE EXPERIENCE UPDATE:

The following serious adverse experiences became available after the submission of the NDA:

1. IND Submission of 25 May 1982. There were two deaths in a comparison of midazolam and diazepam administered intravenously for bronchoscopy. Both deaths involve patients who received midazolam. Neither complication appears reasonably associated with the administration of test drug. The Investigator is Paul A. Kvale, M.D., Head, Pulmonary Medicine, Henry Ford Hospital, Detroit:

The first case involves a 65 year old female who underwent bronchoscopy, which included use of test drug midazolam, on an outpatient basis for the diagnosis of progressive shortness of breath with a productive cough. As a result of this workup, a diagnosis of squamous cell carcinoma of the lung was made; she also had chronic obstructive pulmonary disease. Some time lapsed before hospitalization (time interval uncertain) with a diagnosis of pneumonia, in addition to the above. Hospitalization was directed towards palliation of respiratory failure with infection. The patient died seven days after the bronchoscopy. The clinical impression was that the primary cause of death was disseminated carcinoma. No autopsy was performed.

The second case involves a 48 year old male who was bronchoscoped on 8 FEB'82 because of a chief complaint of lower anterior wall chest pain, bilateral but worse on the left side. X-ray revealed a density, compatible with neoplasia, in the right upper lobe; there were also bilateral pleural based densities and a fracture of the left fourth rib. Bronchial washings revealed squamous cell carcinoma. Radiation therapy was started. The patient rapidly deteriorated, the neoplasia complicated by hypercalcemia. The patient expired on the ninth hospital day, four days after bronchoscopy in which test drug midazolam was administered. Final clinical diagnosis was: Squamous cell carcinoma of the lung, complicated by hypercalcemia secondary to the tumor. Postmortem examination was refused.

2. THIS JUST RECEIVED: (intramuscular midazolam) submission dated 20 June 1984.

ROCHE, New Jersey, was notified on 15 June 1984 by Roche of Welwyn & Lesle that a 21 year old male medical student had developed thrombocytopenia which progressed to pancytopenia and finally aplastic anemia after participating in a pharmacokinetic study in Cardiff, England (Dr. Richen's research unit). The subject received midazolam orally, intravenously, intramuscularly and "PR" in October 1983. Thrombocytopenia developed in January 1984 and the rest of the picture followed. The patient is in critical condition and is not expected to live.

This is all the information that is available at this time (26 June 1984). Medical records will be forwarded upon receipt. There are insufficient data to try and determine drug relationship to this incident.

This reviewer joins ROCHE in awaiting more data and will not render an opinion about test drug relationship at this time. No recommendations, based upon this case, will be made at this time; it is obvious that such a determination will be made prior to approval.

PHARMACOKINETICS:

MFN-120 has asked the Division of Biopharmaceutics to review the Pharmacokinetic Data. I will gladly leave the definitive review to these people. Here are some notes I have made for my own use, because I hopefully will not always have ~~the~~ ^{the 2 room full} jackets ~~to~~ refer to and plan to use these notes instead. None of this is intended as definitive proof of anything but I may use these notes while reviewing the package insert, pending concurrence of the Division of Biopharmaceutics.

"PIVOTAL" STUDIES:

ROCHE has nominated eight Pharmacokinetic Studies as "Pivotal". Here are some notes on these eight studies:

1. Joseph R. Bianchine, M.D., Ph.D. Chairman, Dept. of Pharmacology, Ohio State College of Medicine, Columbus. Eighteen (18) volunteers underwent testing of 7.5 mg midazolam hydrochloride IV, 7.5 mg IM, 15 mg oral solution of midazolam and 15 mg oral tablet midazolam in an open randomized four-way crossover study with one week washout period between doses. Bioavailability was 94% IM, 38% by oral solution and 41% by tablet. The mean times of peak plasma concentrations were observed to be 0.44, 0.73 & 1.04 hours following IM, oral solution and tablets respectively.

The elimination half life ($T_{1/2\beta}$) was 2.5 hours for IV midazolam and 2.8 hours for IM midazolam. The area under the curve for IV and IM midazolam are not significantly different.

The total body clearance (TBC) following IV administration was a mean of 0.37 L/kg/hr (range 0.24-0.52 L/kg/hr). The volume of distribution ($V_{d\beta}$) following IV midazolam was a mean of 1.64 L/kg (range 0.95-3.14 L/kg).

2. Michael Melvin, M.D., Univ. Calif., San Francisco.

Midazolam maleate solution.

Doses of 0.15 mg/kg (n = 4), 0.3 mg/kg (n = 4), 0.45 mg/kg (n = 4) & 0.6 mg/kg (n = 5) were administered intravenously at a rate of 0.075 mg/kg/minute.

a. Total body clearance (L/kg/hr)—mean followed in parentheses by range:

0.15 mg/kg—0.39 (0.3-0.51)
 0.3 mg/kg—0.51 (0.4-0.6)
 0.45 mg/kg—0.37 (0.22-0.52)
 0.6 mg/kg—0.36 (0.15-0.56)

b. Elimination half life (hours)—mean followed in parentheses by range:

0.15—3.9 (2-12.3)
 0.3—3.6 (2.3-5.8)
 0.45—3.0 (2-5.2)
 0.6—5.6 (4.9-11.2)

c. Volume of distribution (L/kg)—mean followed in parentheses by range:

0.15—3.21 (1.44-6.62)
 0.3—3.13 (1.74-5.04)
 0.45—1.67 (1.31-2.19)
 0.6—2.87 (2.22-3.98)

The metabolite, 1-hydroxymethyl midazolam, appeared at maximum concentration of 8.3-30 ng/ml within 0.22-1 hours after the intravenous dose. $T_{1/2\beta}$ ranged from 1.4-3 hours. This part of the summary is less clear than the rest and means are not provided.

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3. Robert J. Fragen, M.D., Northwestern.

Five volunteers received 2 doses each under [redacted] ascending dose conditions as part of an investigation that also included gathering of pharmacological data. The two doses, received by each subject, were 0.05 mg/kg IM and 0.075 mg/kg IM midazolam hydrochloride.

The maximum plasma concentration (C_{max}) was a mean of 31 ng/ml (range 25-35 ng/ml) for 0.05 mg/kg dose and 68 ng/ml (range 42-103 ng/ml) for the 0.075 mg/kg dose. Time to C_{max} was a mean of 0.43 hours (range 0.25-0.75 hrs) for the 0.05 mg/kg dose and 0.23 hours (range 0.17-0.33 hrs) for the 0.075 mg/kg dose.

Terminal half life was a mean of 2.6 hours for the lower dose (range 2-3.4 hrs) and a mean of 2.1 hours for the higher dose (range 1.7-2.6 hrs).

Total body clearance was a mean of 0.45 L/kg/hr (range 0.35-0.59) for the lower dose and 0.44 L/kg/hr (range 0.34-0.54) for the higher dose.

The volume of distribution in the post distributive phase was a mean of 1.71 L/kg (range 1.61-1.83) for the lower dose and 1.36 L/kg (range 0.83-1.92) for the higher dose.

The protein binding determined in the one hour plasma sample following the higher dose of 0.075 mg/kg was a mean of 97.0% (range 95.9-97.6%).

4. Frank H. Sarnquist, M.D., Director, Palo Alto Analgesic Research, Veterans Administration Hospital, Palo Alto, CA.

Five healthy male volunteers received an initial intravenous infusion of 10.5 mg total midazolam maleate over 15 minutes, followed by a constant rate infusion of 15.75 mg total over 3.75 hours. Blood concentrations reached a plateau within 30 minutes after start of the infusion and remained relatively constant to the end of the infusion (64.9-85.2 ng/kg). After termination of the infusion, blood concentrations decreased biexponentially with elimination half lives ranging from 1.6-1.9 hours. Total body clearance was 762-995 ml/minute (note different units from the above). Urinary excretion of the conjugated 1-hydroxymethyl metabolite accounted for 46-52% of the dose over 24 hours.

The minimum concentration associated, but not correlated, with subject awakening ranged from 38.2-70.9 ng/ml (estimate).

5. Donald Rothfield, M.D., Newark Beth Israel Medical Center, Newark, NJ.

Eleven patients with a history of congestive heart failure and dyspnea on exertion received a single 5 mg intravenous dose of midazolam maleate (dose calculated as free base). Mean age was 54 years (range 33-67 years). Mean weight was 84 kg (range 64-116 kg).

The elimination half life for midazolam was a mean of 6.5 hours (range 4.6-11.8 hours).

The total body clearance in the post distributive phase was a mean of 0.48 L/kg/hr (range 0.25-0.95).

The volume of distribution in the post distributive phase was a mean of 4.53 L/kg (range 2.26-6.26).

pharmacokinetics---page three---

Some effort was made to do a blood concentration-time profile of 1-hydroxymethyl midazolam, the major metabolite, but this did not afford definitive evaluation. What was learned was that the time to maximum concentration was 0.43 hours mean (range 0.25-1.5 hours) and that the maximum concentration was 5.3 ng/ml mean (range 2.5-9.7 ng/ml).

The sponsor's staff concludes that the half-life of elimination is increased in congestive heart failure patients. They also note that the volume of distribution in the post-distribution phase is approximately 1.5 to 2 fold greater in these patients than in healthy subjects. These findings also indicate that the relative amount of 1-hydroxymethyl midazolam following administration of midazolam to congestive heart failure patients is similar to the relative amount of this metabolite formed following drug administration to healthy subjects.

Beyond the fact that sedative and hypnotic effect of midazolam was not unusually prolonged in this study, I can find no precise information on recovery in the summary. The sponsor's final conclusion is that the presence of congestive heart failure should not influence the single dose administration of midazolam.

6. Robert J. Fragen, M.D., NORTHWESTERN.

This was a study of 0.2 mg/kg midazolam hydrochloride for induction of general anesthesia, administered over 30 seconds. Twelve patients were aged 18-30 years and these data were compared to 12 patients over 49 years of age (range 49-60 years); mean age for the first group was 25 years and mean age for the second group was 54 years. Clinical aspects of this study have been summarized under Protocol 2192; differences are noted but these are subtle; these data led me to conclude that, over the age range of 18-60 years, use of midazolam need not be modified because of age. Patients were all female, scheduled for short surgical-diagnostic gyn. procedures.

Elimination half-life was a mean of 2.6 hours in the younger population (range 1.6-6.6 hours) and a mean of 3.8 hours in the older population (range 2.6 to 8 hours).

Total body clearance was a mean of 0.42 L/kg/hour (range 0.25-0.77) in the younger patients and 0.39 L/kg/hour (range 0.26-0.49) in the older subjects.

The volume of distribution in the post-distributive phase was a mean of 1.67 L/kg in the younger patients (range 1.09-2.97) and a mean of 2.43 L/kg (range 1.36-5.68) in the older patients.

The sponsor concludes that age does not significantly alter the pharmacokinetic profile of midazolam in female patients at the dose studied. To this I would only add: at the ages studied and compared.

pharmacokinetics, page four-----

7. F. Gilbert Mc Mahon, M.D., Head, Therapeutics Section, Dept. of Medicine, Tulane University, New Orleans.

This study was conducted in 12 male patients, aged 21-59 years (mean 36 years), described as clinically having stabilized cirrhosis, without clinically apparent ascites, and with normal renal function as determined by creatinine clearance. Weight mean 71.4 kg (range 55.4-86.3 kg). Five mg of midazolam maleate was administered intravenously over 2 minutes via intravenous line.

Mean terminal half life ^{of midazolam} was 2.41 hours (range 1.55-6.85 hrs.).
Mean terminal half life of 1-hydroxymethyl midazolam was 2.19 hours (range 1.64-4.69 hrs.).

The mean total body clearance for midazolam was 0.56 L/kg/hr (range 0.25-1.12 L/kg/hr). The mean volume of distribution in the post-distributive phase for midazolam was 1.77 L/kg (range 1.10-3.18 L/kg).

The maximum concentration of 1-hydroxymethyl midazolam was also determined: mean 7.9 ng/ml, range 5.0-14 ng/ml.
The mean time to maximum concentration for 1-hydroxymethyl midazolam was 0.76 hours (range 0.28-2.0 hours).

It is also interesting to note that these subjects did not lose response to spoken word. They did cease counting at 1-12 minutes (mean 5) after start of medication. In most subjects, sedation and drowsiness were observed. Complete arousal (criteria not discussed in summary) took 38 minutes (mean) and full orientation was judged to have returned in 43 minutes (mean).

The sponsor concludes that the pharmacokinetic profile is the same in these patients as in normal subjects, following the administration of 5 mg midazolam maleate intravenously to patients with hepatic dysfunction. Formation rate limitations prevented an assessment of the actual half life for the metabolite (plasma concentration curves run parallel until the limits of assay are reached for the metabolite at 4 hours---limits of assay for midazolam are reached at about 16+ hours).

8. Joseph Gerald Keves, M.D. & H.R. Vinik, M.D., Univ. of Alabama, Birmingham. Fifteen patients with renal failure (13 chronic and 2 acute) in need of dialysis, who were scheduled for elective creation of an arteriovenous shunt prior to chronic hemodialysis, were enrolled in this study. Mean age was 49 years (range 24-68 years), 6 males & 9 females. These patients received 0.2 mg/kg of midazolam maleate, calculated as the free base; rate of administration is unclear from the summary.

Mean elimination half-life was 3.3 hours (range 1.4-8.3).
Mean total body clearance was 0.60 L/kg/hour (range 0.36-1.10).
Mean distribution in the post-distributive phase was 3.4 L/kg (range 1.51-5.74).
The plasma protein binding of midazolam in the one hour sample (equilibrium dialysis technique at 37°C) was a mean of 97.1% (range 95.3-98.9%).

The mean time to orientation (time & place) was 70 minutes (range 30-125 minutes). ^{Circulatory} vital sign changes during the study were mild (less than 30% but greater than 20%). Respiratory signs were typical for induction of general anesthesia.

pharmacokinetics, page five---

In addition, an overall Pharmacokinetics summary is provided in Volume 1.4 of the NDA. This volume is at times hard to follow. The following information therein should be briefly cited:

1. There are 10 studies of pharmacokinetics after single intravenous administration of midazolam (maleate or hydrochloride solutions). In eight of these studies, $T_{1/2\beta}$ ranged from 1.6-2.8 hours. One published study (J.W.Dundee, et. al., Anaesthesia 35:454,1980) there is brief mention of a half-life "between 60 and 90 minutes"; this is shorter than the results of the other studies but it is a bit hard to follow and may be misleading if cited as the lower time limit in the package insert. Another reference providing a low lower limit is actually a publication by Roche staff addressed mainly at method of analysis.
2. In longer infusion studies, $T_{1/2\beta}$ may increase to 4-5.6 hours in linear dose related fashion.
3. The major metabolite recovered in plasma and in urine (urine in the glucuronide form) is 1-hydroxymethyl midazolam.

Minor metabolites recovered in the urine include 4-hydroxymidazolam and 1-hydroxymethyl-4-hydroxymidazolam. There seems to be little additional information on these minor metabolites.

In studies which follow the appearance of 1-hydroxymethyl midazolam in plasma, appearance is relatively rapid following infusion of midazolam. After equilibrium is reached, concentration curves are relatively parallel until the concentration of the metabolite approaches the limits of analytical technique in about 6 hours. Midazolam takes about 8-12+ hours to reach the limits of analysis (16+ hours in patients with congestive heart failure).

4. I found no animal data of the narrow variety that may be needed to supplement human pharmacokinetics in the preparation of information for clinicians in Volumes 1.4, 1.16 or 1.17, the Pharmacokinetics volumes. I would particularly like to know if any midazolam metabolites are excreted into the gastrointestinal tract through the biliary tract.

Linda Stehling, M.D., Dept. of Anes., Syracuse, N.Y.
Protocol 830B

of midazolam maleate solution

This was an early study, by a highly regarded clinical investigator. Doses were not well known at the time, and even this investigator could not overcome the fact that the study employed too low a dose. Induction was as in previously summarized studies, mainly the test dose was administered, two minute wait, 25% more drug, 2 minute wait, etc. All patients were unpremedicated.

Open protion: The initial dose of 100 ug/kg proved too little in 7 patients out of ten, so the dose was elevated to 150 ug/kg in the remaining 3 patients. Even then, 5/10 patients required thiopental to complete induction.

Double-blind randomized: 20 additional patients received the initial dose of 150 ug/kg midazolam maleate. Nine of these 20 required thiopental to complete induction. The dose employed, combined with the usual two minute waits between increments proved too much. The mean total dose in those cases which were eventually successfully induced with midazolam (11/20 or 55%) was 190 ug/kg. The comparative drug was methohexital in the initial dose of 1 mg/kg (n = 30). This dose also proved inadequate in 20/30 patients or 66.6%. Mean total dose in the 10 successful cases was 1.18 mg/kg. This may not be the fault of the drug, but rather of the methodology, since methohexital is shorter acting than thiopental when used for induction; the 2 minute waits probably proved too much. As for midazolam, thiopental was used to complete induction in the unsuccessful cases.

Impairment of recall was determined in successful induction cases only, but in view of the poor results of the study it seems meaningless for this reviewer to tabulate results. Much more useful information can be obtained from the more successful studies and the better methodology which evolved later.

SAFETY: There were no unusual safety problems revealed in this study. Forty percent of the methohexital patients had a moderate increase in heart rate during induction, as did 10% (2) of the midazolam maleate patients. One midazolam patient had a severe increase in heart rate (greater than 50%), as did 3 methohexital patients.

REVIEWER'S IMPRESSION: The dose of 100 ug/kg and the dose of 150 ug/kg, as administered in this and other protocols, proved inadequate for induction of anesthesia in unpremedicated patients. Nothing else of importance was learned.

Fragen, No. 830A

This was an early study, involving midazolam maleate. The intent was to have a double blind comparison of midazolam (n = 25), diazepam (n = 24) and thiopental (n = 26) for induction of general anesthesia in 75 ASA Status I, II & III females undergoing elective surgical procedures. Premedication was with only atropine 0.4 mg IM. The initial doses were: midazolam 150 ug/kg, diazepam 300 ug/kg and thiopental 3 mg/kg. If patients were not asleep in 2 minutes, increments of 25% of the initial dose were administered every two minutes until the desired results were produced. Injections were over 15 seconds. Maintenance was with drugs of clinician's choice, excluding droperidol & test drugs. The doses turned out to be too low for midazolam, and also diazepam. The mean dose of midazolam for induction was 179 ug/kg, the mean time of induction was 162 seconds, but the range of induction time was 60-560 seconds. The time of 560 seconds is beyond practical range in every day clinical practice. The ~~mean~~ dose range for midazolam was 138-288 ug/kg.

The mean dose of diazepam was 363 ug/kg, range 280-521 ug/kg, time 171 seconds mean (range 45-480 seconds).

The mean thiopental dose was 3.12 mg/kg, range 2.52-3.87 mg/kg, time 81 seconds mean (range 30-180 seconds).

There were specific comments made about the lightness of anesthesia (mumbling, blinking, pronation, etc.) in 15/25 of the midazolam cases (60%), 8/24 of the diazepam cases (33.33%) & 4/26 of the thiopental cases (15.4%).

Impairment of recall was tested, but not by the same methodology as the other Fragen studies summarized to date. After premedication, the previously cited memory card was shown to the patients. Approximately 24 hours later, patients were questioned about their recall of the memory card, leaving room to go their to the operating room and entering the operating room; retrograde amnesia was considered present if they could not remember any of these three items. At the same time, patients were asked about recall of the recovery room; anterograde amnesia was considered present if there was no recall of the recovery room. Retrograde amnesia was generally absent (m = 3/25, d = 0/24 & t = 3/26). Anterograde amnesia was generally absent (m = 6/25, d = 8/24 & t = 3/26). The sponsor feels that this method was not highly sensitive. In comparison with the methodology of Fragen 2085A and 2192, previously summarized by me, I would agree.

Pain on injection: m = 8/25 or 32%, d = 16/24 or 66.66% & t = 6/26 or 23%. Venous irritation on followup: m = 3/25 or 12%, d = 5/24 or 20.8% & t = 2/26 or 7.7%. The higher incidence of pain on injection of diazepam is in keeping with clinical experience with the water insoluble formulation; it is hoped that water soluble midazolam will greatly decrease this problem. Still, diazepam in this study was not associated with an unusual incidence of venous irritation on followup.

There was a scattering of mild and moderate (as previously defined) vital sign changes during induction, following no particular pattern. One thiopental patient manifested a severe (greater than 50% or requiring treatment) increase in heart rate during induction; this was the only such case.

Fragen 830A, page 2wo----

Patient (200 lb male aged about 58 years at time of surgery in 1977) received a total of 17 mg of midazolam for induction of anesthesia (about 190 ug/kg) and is listed as having afterwards manifested a "severe" drop in blood pressure; the case report is not very enlightening except for suggestions between the lines that this was no big deal. The patient had a preoperative diagnosis of Pneumaturia, Hematuria and Nocturia. The procedure was Cystoscopy, Bladder Biopsy and "PNB" (an abbreviation unfamiliar to me and to a Staff Urologist, who suggested that it might mean Prostatic Needle Biopsy????). ~~Induction was achieved with 17 mg of midazolam (about 190 ug/kg)~~ Pre induction blood pressure was 122/74 and pulse was 110. After induction the blood pressure declined to 94/45 and pulse rose to 115/minute. ~~When surgery started the blood pressure was 85/60, but by then enflurane had been added. Blood pressure then quickly rose to preoperative level but moderate increases and decreases were noted during surgery. The "severe" blood pressure drop was judged "probably related" to administration of test drug. The duration of drop was about 20 minutes. It appears that no treatment was required.~~

Pneumaturia can be related to any gas forming bacteria in the urinary bl and glycosuria is a predisposing factor in the face of infection. The patient is not listed as a Diabetic but a preoperative fasting blood sugar was 160mg/100 ml (I cannot locate a urinalysis on the case report). Our Staff Urologist (C.R.) notes that Pneumaturia is not reasonably associated with enterotoxins that would cause a transient drop in blood pressure.

Again, this appears to be no big deal. I note also that this case took place to be used in in 1977, before a full plan for data gathering & subsequent studies had been developed. Then why did I write all of this? Because I asked the Staff of ROCHE (Feb'84) to provide me with patient identification for all cases of "severe" blood pressure drop on Induction (not maintenance). They could come up with only three such cases; even allowing for missing a case or two this is ~~an impressive number~~ a small number. The other two cases are in Reves Study No. 1092A.

REVIEWER'S IMPRESSION:

These data support using larger doses of intravenous midazolam initially for induction than were used in this study. The initial dose of 150 ug/kg in unpremedicated patients (atropine excepted) was not enough when considering also the time required for induction under the conditions of this experiment. Impairment of recall was studied by better methodology in other studies which came later, such as Fragen 2085A & 2192.

Despite one midazolam patient listed as having "severe" blood pressure drop on induction of anesthesia, judged probably drug related, there appear to be no unusual safety problems revealed in this study (see above).

Richard N. Terry, M.D., Chief, Dept. of Anes., Buffalo General Hospital, Buffalo, N.Y.
Study 1012

I learned very little from this study, except that this investigator team found an initial dose of 150 ug/kg midazolam maleate to be insufficient for induction in patients premedicated mainly with atropine 0.01 mg/kg and meperidine 1 mg/kg IM one to two hours before anticipated surgery.

Fifty one ^{adult surgical} patients participated. The intent was to induce anesthesia in half with midazolam 150 ug/kg, wait 2 minutes and then add the usual 25%, etc. as in other studies. The comparative drug was to be thiamylal 3 mg/kg. In actuality most comparative patients (22/25) received thiopental instead of the planned thiamylal. Instead of using Roche randomization code, the investigator team used their own randomization code. The intent was also to use test drug as part of the regimen for maintenance of anesthesia; in actuality, only 3 midazolam patients and 2 thiobarbiturate patients received test drug during maintenance and no records were kept of other medication. Time of surgery (mean) was 64 minutes in the midazolam group and 82 minutes in the thiobarbiturate group, suggesting that maintenance intravenous agents would have been required. In short, this turned out to be an open study and a rambling one at that. It would be a waste of time to do a thorough summary or even to cite all protocol deviations.

Instead of 3 mg/kg, the mean induction dose of thiobarbiturate was 5.35 mg/kg (22 = thiopental and 3 = thiamylal). No increments were needed in this group. In contrast, the mean total dose of midazolam maleate solution was 231 ug/kg and induction time was 215 seconds. Mean time for induction in the thiobarbiturate group was 139 seconds, an unfair comparison since doses were double those initially administered in most other studies of induction.

No unusual safety problems were revealed in this study.

Protocol 943, Mia Parsonnet, M.D., Clinical Pharmacology Unit, Newark Beth Israel Medical Center, Newark, NJ.

This was a study in 4 healthy male volunteers, aged 23-39 years. They received a single intravenous dose of 0.15 mg/kg midazolam. Ejection fraction was evaluated by the M-E-F method, showing varying decreases, with maximum decreases per subject varying from 8% to 19%. See copy of table below, obtained from the sponsor's summary in Volume 1.14

TABLE III
Ejection Fraction

	Subject Number			
	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>
Immediate decrease	NS	NS	NS	NS
Time of maximal change (minutes)	3	6	55	35
Maximal decrease	19%	19%	13%	8%
Average decrease	13%	5%	4%	0
Decrease at end of observation	13%	15%	4%	0
NS = not significant				

Serial blood and plasma concentrations were obtained. Midazolam disappeared almost completely by 12 hours. The elimination half life ranged from 1.46-2.68 hours (mean 2.06 hours).

SAFETY: There were no real safety problems noted; all safety information is generally more complete from the later developing mass of clinical data. It is interesting to note that one volunteer complained of a feeling of fuzziness in the head. Other adverse observations of note, one each, include: nystagmus, conjugate deviation & rambling speech. There was no pain or irritation at the injection site for midazolam maleate.

Protocol 1062A, H. Peter Blumenthal, M.D., Clinical Pharmacology Unit,
Newark Beth Israel Medical Center, Newark, NJ.

Seven healthy volunteers, aged 25-30 years participated in a randomized single-blind crossover study of the ventilatory response to carbon dioxide stimulation of midazolam 100 ug/kg i.v. and thiopental 2000 ug/kg i.v. Subjects were generally sedated but responsive during the test period. Carbon dioxide sensitivity was tested according to the method of Read. A 5 liter bag with 7% CO₂ and 93% O₂ was used, with changes in ventilation recorded every 30 seconds for five minutes. Carbon dioxide was stepped up 8 mmHg during testing. The test was performed 1 hour before test drug administration, immediately after test drug administration, 15 minutes later, 30, 45, & 60 minutes after test drug administration.

Under the conditions of this experiment, there were no significant changes in the slope (liters/minute/unit change in mmHg CO₂) after midazolam administration. By 15 minutes after thiopental administration, the slope was steeper (more Liters per minute per unit change upward in mmHg CO₂) than baseline; this persisted for the one hour of testing. Baseline differed between the two drugs, about 10 L/minute/mmHg for thiopental and about 8 L/minute/mmHg midazolam.

SAFETY: Tenderness at the intravenous site was noted in one subject the day after midazolam maleate injection. The same goes for one subject after receiving thiopental. The other subjective and objective observations serve no useful purpose in the overall evaluation of this NDA, being later eclipsed by the mass of clinical data.

REVIEWER'S COMMENTS: I wouldn't worry about this study. Go right to Study # 2138, T.C.Smith.

SUMMARY, FOR THE RECORD ONLY, OF PROTOCOL NO. 2368:

Raymond Glassenberg, M.D. and Robert J. Fragen, M.D., Northwestern.

This randomized, double-blind, study compared midazolam 0.8 mg/kg IM, Morphine 0.1 mg/kg IM and midazolam 0.04 mg/kg IM with morphine 0.05 mg/kg IM for pre-anesthetic medication. Only 13 patients participated by the time of submission of the NDA, therefore, no analysis for efficacy is feasible. There were not safety problems encountered during the conduct of this study. Occasional changes in vital signs were noted during preanesthetic period and during the induction phase of the study.

Jeffrey Gross, M.D., Veteran's Adm. Hosp., Philadelphia.
Study # 2347

This study was ongoing at the time of NDA submission and as yet inconclusive as to dosage recommendations or efficacy, fifteen patients having participated at the cutoff point. Eight received midazolam for induction and seven received ketamine (ASA Risk III patients undergoing elective surgery).

SAFETY: Nothing unusual for induction and maintenance of anesthesia was noted. One patient in each group manifested phlebitis at the time of postoperative evaluation. Although technically listed as "possibly" drug related, it should be noted that in both cases a new intravenous infusion was started at the site of test drug administration while the patients were in the recovery room.

There were two cases of prolonged depressed consciousness after anesthesia and surgery in the midazolam group. The dose of midazolam in each was standard, 250 ug/kg for induction. In the case of patient _____ the patient remained asleep and unresponsive for 90 minutes and was disoriented and lethargic for another 90 minutes; this _____ responded to physostigmine 0.2 mg accompanied by glycopyrrolate 0.2 mg, both intravenously. The results were a profound increase in level of consciousness and orientation as to place and time, which apparently persisted afterwards. None of the classical drugs known to respond to physostigmine were administered (mainly, but not only, anticholinergics known to cross the blood-brain barrier).

The other case also involves none of the other drugs known classically to respond to intravenous physostigmine in the face of central nervous system problems. The patient had about one hour of extreme sleepiness and lethargy in the recovery room. He responded to 2 mg physostigmine and 0.2 mg glycopyrrolate intravenously with awakening and orientation as to time and place. The response was only partial because some lethargy and sleepiness persisted for 12 hours after anesthesia and surgery. The dose of midazolam was a standard 250 ug/kg for induction.

No definitive conclusions on use of physostigmine for midazolam related central nervous system depression and lethargy can be made on the basis of these two cases. Physostigmine is classically used to treat central nervous system anticholinergic manifestations. Some of the drugs which apparently respond are not really central anticholinergics; diazepam and other benzodiazepines come to mind and midazolam belongs to this group of drugs. Glycopyrrolate is used to counteract the muscarinic effects of physostigmine because glycopyrrolate either does not cross the blood-brain barrier or does so only in trace quantities. Any labeling action will have to be based on the latest thinking about use of physostigmine, a pre-1938 drug that is more administratively suitable to HFN-160 (Neuropharmacological Drugs) than to other divisions.

The complete clinical account (investigator's account) is appended as page two of the review of this study. It is derived from page 91 of Volume 1.30 of the NDA.

Patient A 60-year-old 52 kg man was scheduled for esophageal resection. He had previously undergone bilateral radical neck dissections for laryngeal carcinoma, with no apparent anesthetic complications. He had chronic obstructive airway disease and hypothyroidism which was treated with 0.05 mg thyroxine daily. He had also lost twenty pounds in the last year. Fifty minutes before induction of anesthesia, he received 5.2 mg morphine and 0.21 mg glycopyrrolate, im, for premedication. While breathing oxygen, 13.1 mg midazolam (0.25 mg/kg) iv resulted in loss of response to commands and of voluntary movements, but the eyelid reflex remained active; an additional 2.6 mg (0.05 mg/kg) of midazolam abolished this reflex. Ten min later, the patient moved in response to surgical stimulation, and was given 100 mg thiopental, iv. Twenty-five min after the initial injection of midazolam, surgery ended. In the post-anesthesia room he remained asleep and unresponsive while breathing 40 per cent oxygen from a T-piece. Ninety min later, he began to open his eyes on command, however, he remained disoriented and lethargic for another ninety min (3 h after induction of anesthesia), at which time 0.2 mg naloxone given iv had little effect on his level of consciousness or degree of orientation. Five min later, 2 mg physostigmine and 0.2 mg glycopyrrolate were given iv, which resulted in a profound increase in the level of consciousness and orientation to place and time. He was then discharged to his room.

Patient A 66 kg, 58-year-old man with mandibular atrophy was scheduled for vestibuloplasty. His medical problems included severe chronic obstructive airway disease requiring treatment with terbutaline and theophylline, mild congestive heart failure requiring digoxin therapy, and previously resected carcinomas of the colon and bladder. Forty-five min before induction of anesthesia, he received 6.6 mg morphine and 0.26 mg glycopyrrolate im. Midazolam, 16.5 mg (0.25 mg/kg), induced anesthesia, which was maintained with enflurane, nitrous oxide, and oxygen. Succinylcholine provided relaxation for endotracheal intubation, while 7.2 ml of 1 percent lidocaine with 1:100,000 epinephrine were injected locally by the surgeons at the beginning of surgery. Enflurane was discontinued 2 h after induction of anesthesia, nitrous oxide being discontinued twenty min later, at the end of surgery. On arrival in the post-anesthesia room 2.5 h after induction of anesthesia, the patient was very lethargic. Analysis of arterial blood gases with oxygen 4 l/min administered by nasal cannula revealed a P_{aO_2} of 83 mmHg, P_{aCO_2} of 60 mmHg, and a pH_2 of 7.29. One hour later, the patient remained lethargic and disoriented; 2 mg physostigmine with 0.2 mg glycopyrrolate was given iv. Within minutes, he awoke and was oriented to person and place. P_{aO_2} was then 60 mmHg, P_{aCO_2} 52 mmHg, and pH_2 7.32. He remained in the post-anesthesia room for an additional four hours, at which time he was moved to the intensive care unit for continued observation. He was somewhat lethargic although he remained oriented to person and place. Twelve hours after induction of anesthesia, he was fully awake; P_{aO_2} was 66 mmHg, P_{aCO_2} 45 mmHg, and pH_2 7.36 with a FI_{O_2} 0.24 by venturi mask.

Summary of Pooled Protocol No. 2245 (Incomplete at time of submission NDA)

Investigators: Carl P. Weiner, ^{MD,} Stephen R. Richards, ^{MD,} Ohio State Univ., Columbus
Raymond B. Wait, M.D., Jefferson Davis Hosp., Houston
J. Patrick Lavery, M.D., Univ. of Louisville

The objective was to determine whether or not midazolam 0.07 mg/kg IM enhanced the pain relief of oral codeine 30 mg. Postpartum patients with episiotomy pain were selected to participate and there were 58 participants out of a planned 120 at the time of submission of the NDA. Group sizes (4 groups, midazolam, codeine, midazolam plus codeine and placebo) are too small to make definitive conclusions at this time. No claims are made in the application (draft package insert) so no review for EFFICACY need be conducted.

There were no real safety problems noted. One codeine patient had drowsiness listed as an adverse experience. One midazolam plus codeine patient experienced pain at the injection site; another patient in this group complained of muscle stiffness for 2 days after injection.

Hematological and biochemical screening revealed no laboratory abnormalities reasonably associated with administration of test drugs.

Protocol 2066A, Carter M. Ballinger, M.D., University of Colorado, Denver.

This study had just started good when the NDA was submitted. It is intended to compare midazolam and thiopental, with and without meperidine and atropine. At the cut off for NDA submission, there were five cases. No conclusions can be reached. There were, for all practical purposes, no safety problems encountered.

Protocol 2146B

Robert Vaughn, M.D., Arizona Health Science Center, Tucson.

This study was terminated after 12 cases. The reason given in the summary was because of reorganization of sponsor's projects. The study was a comparison of midazolam 200 ug/kg and ketamine 1 mg/kg for induction in patients premedicated with glycopyrrolate 4 ug/kg. ASA III patients participated. In practice, all except one are listed as having cancer, usually disseminated. The investigator turned out to be unusually observant, making adverse observations on every case. He felt that at the first sign of trouble it was wisest to complete induction with a known drug, rather than the blinded test drug; thiopental was elected to complete inductions. He was so good at spotting the first sign of trouble that only 2/6 patients in each group had induction completed with test drug. The rapidity of the investigator's decision to switch to thiopental, regardless of the merit, precludes any conclusions about dosage based upon this study.

SAFETY:

Your reviewer noted much in the way of listings of various skeletal muscle manifestations during induction of anesthesia, in both groups. No definitive conclusions could be reached from the sponsor's summary. Since this is the only study encountered so far (26 April 1984) with such adverse observations, I felt that I had to examine the case reports. Here is some of the information I noted on the case report forms (note that skeletal muscle activity includes tonic/clonic movements, agitation, phonation, etc.):

Ketamine Group	male patient Patient _____, Bladder Ca. with Metastasis, scheduled for Colon Resection. Manifested purposeless movements on induction, judged severe and probably test drug related. The investigator(s) felt that it was best to switch to a known drug (in this case thiopental) to complete induction. Male patient.
Midazolam Group	female patient Patient _____, Judged postoperatively to be terminal, source not stated but probably pelvic (Radium Implant-Pelvis-for Carcinoma). She manifested purposeless movements on induction, mild in severity, probably related to test drug administration. Managed by finishing induction with halothane.
Midazolam Group	Patient _____ Terminal Carcinoma, source not stated; female patient. Purposeless movements noted on induction, judged mild and probably test drug related. Induction was completed with thiopental.
Midazolam Group	Patient _____ Male patient for Ileal Loop for Bladder Carcinoma. Purposeless movements noted on induction, judged mild and probably test drug related. Induction completed with thiopental, a known drug.
Ketamine Group	Patient _____ Female patient with Carcinoma of the Cervix. Surgery is listed as Colostomy; the patient is listed as being judged ASA Risk III because of cachexia, malnutrition and anemia. She manifested agitation and phonation during induction, severe in nature and judged possibly related to drug administration. Thiopental was used to treat this adverse observation but induction was apparently completed.

Ketamine
Group

Patient Female patient with Adenocarcinoma, source not stated. Procedure was essentially Examination Under Anesthesia. She had extensive therapy, weakness of skeletal muscles and myasthenoid syndrome (Eaton-Lambert); thus, she was judged ASA Risk III. She manifested increased phonation on induction, judged moderate in severity and possibly related to test drug administration. No treatment was required.

Ketamine Gr.

Patient ~~(Sorry that this one is out of sequence, I missed this one the first time around the case reports and I don't have a word processor to move information around with)~~ This is the only patient in this study not specified as a cancer patient. Male with a diagnosis of Bladder Neck Obstruction (otherwise not specified) for Trans-Urethral Resection of the Prostate. The clinicians judge him to be ASA Risk III because of "Asthma". Chronic medication included aminophylline, terbutaline, prednisone and hydrochlorothiazide (for hypertension). He manifested purposeless movements on induction, transient in nature and not requiring treatment. These movements were judged mild and probably related to test drug administration.

Patient Midazolam group. Female with Ovarial Carcinoma, scheduled for Laparotomy. Judged ASA III because of disseminated carcinoma and cardiomyopathy. Chronic medication included adriamycin (potent anti-neoplastic drug known to be associated with cardiomyopathy), cytoxan, cis-platinum & lithium. Moderately severe purposeless movements were noted during induction, managed with use of thiopental and lasting "minutes" (smallest time quantity on check list). This was judged probably related to test drug administration. The investigator lists the thiopental as having been used to complete induction because the patient lightened; it seems that he preferred to use a known drug at the first sign of trouble.

Patient Midazolam group. Female with Lymphoma for Splenectomy. Judged ASA III because of cachexia, lymphoma, hypokalemia and pancytopenia. No real problems, except that mean arterial pressure fell moderately during surgery (previous definition of moderate), but only mildly (also previous definition) during induction. No treatment was required. No skeletal muscle observations (tonic/clonic movements, phonation, such as evasive movements, etc.).

Ketamine Group.

Patient : Male with bladder carcinoma for Cystectomy and Ileal Loop. Judged ASA III because of "Pulmonary: Severe Asthma". Also: Diabetes & hypertension. Chronic medication listed: hydrochlorothiazide only. No problems unusual for general anesthesia noted during induction; the patient developed airway obstruction and apnea, responding in the usual manner to airway insertion and positive pressure ventilation.

Ketamine Group.

Patient Female with Cervical Carcinoma for Laparotomy. Judged ASA III because of rheumatic heart disease, heavy smoking, renal insufficiency, and cachexia. No medications listed. Mild pain was noted on injection of study drug, transient and possible test drug related. Tonic/clonic movements were noted during intubation, treated with thiopental 150 mg. Severity was judged mild and this adverse observation was judged possibly related to test drug administration. Comment from Investigator: "Prior to completed induction, subject's eyes opened and fasciculations were evident---". Succinylcholine was also administered, presumably for intubation, but timing and quantity is not stated. This patient and patient also manifested transient pain on injection.

page three-----

Patient _____ Midazolam Group.

Male with Unresectable Rectal Carcinoma for (?) "Syed Implant Hyperthermia Treatment"
Judged ASA Risk III because of "Pulmonary; Arteriosclerotic heart disease".He manifested tonic/clonic movements on induction (mild, measured in minutes
and treated with thiopental---judged possibly related to test drug administration).)

Also listed: Purposeless movements during induction, mild, measured in
minutes (smallest unit to check) ~~and possibly related~~ and possibly related
to test drug administration. Technically, this is one of the 4/6 midazolam
cases where some other induction drug (thiopental) was used as a known drug
to complete induction. This patient and patient _____ are the only two patients who
manifested pain on injection (transient).

REVIEWER'S IMPRESSION:

Some time was lost looking at case report forms because this reviewer could not
complete the SAFETY review from the sponsor's summary alone. Now it seems that
the investigator was unusually observant and unusually generous with the recording
of adverse observations, usually minor. The two cases (one for ketamine and one for
midazolam) described as tonic/clonic movements on induction also manifested
transient pain on injection; these could have been evasive movements and so might
have been some of the other skeletal muscle adverse observations. Evaluation
of dosage, under this protocol, was not possible because of the unusual caution
of this investigator in switching from the blinded test drug to a known drug
(usually thiopental but sometimes halothane) to complete induction. It is interesting
that these patients, with the possible exception of patient # 3, all had cancer,
usually widespread. I am very puzzled by these observations and feel that there
is something to be learned which is currently eluding me. As of this date (26
April 1984), I can make no drug regulatory recommendation based upon this study.

Young H. Han, M.D., Montefiore Hosp, Bronx, N.Y.

Study 1029A

SUMMARY FOR THE RECORD ONLY.

Let's be brief! This was to be a study of induction and maintenance in patients premedicated with meperidine and glycopyrrolate. The study was to involve 100 patients but it was terminated after 51 cases because of numerous protocol violations and poor record keeping (26 midazolam maleate and 25 thiopental). The record keeping problems are such that no information on dosage recommendations, for the clinician, can be offered as a result of this study. For additional details, see Volume 1.32 of the NDA.

No unusual safety problems were revealed in this study, except that one 93 year old patient who was included in the study was reported as sedated for 4-5 hours after surgery. The patient was in for surgery due to carcinoma of the colon and had a past history of multiple myeloma. Chronic medications included hydrochlorothiazide, Halotestin and flurazepam. The total dose of midazolam for induction was 6.25 mg (142 lbs). An additional 7.5 mg was used during maintenance. Premedication consisted of 70 mg meperidine & .19 mg glycopyrrolate. It is also interesting to note that naloxone 0.4 mg was administered intravenously and that response improved within 3-5 minutes (timing of naloxone not stated). Vital signs were judged stable during the period that the patient appeared over-sedated. In retrospect, this appears to be a case of poor subject selection for such an investigation. Mean age was 66 years in the midazolam group and 51.5 years in the thiopental group. There seems little to be gained by adding this extreme of age onto a general protocol. Another patient received 10 mg for induction and 45 mg for maintenance, for a total of 933 ug/kg, and slept for 4 hours postoperatively. The investigator felt, in retrospect, that the ~~dose was overestimated during maintenance~~ needed maintenance dose was overestimated; there is no reason to argue with that impression.

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Protocol No. 1029C

Robert G. Hicks, M.D., Director of Anesthesia, St. Vincent's Hospital, NYC

SUMMARY FOR THE RECORD ONLY. PROTOCOL VIOLATIONS RENDER THIS STUDY USELESS FOR EFFICACY.

This was supposed to be a study of induction and maintenance with midazolam and thiopental for comparison. The intent was to study 100 patients, but the study was terminated after 46 cases because of the protocol violations (23 midazolam and 23 thiopental).

Some of the deviations:

1. The intent was to administer 150 ug/kg midazolam for induction and then use 25% increments. In actual practice, initial dose varied from 130-340 ug/kg. Incremental injections were not always 25%. Time interval between increments varied. Dosage of thiopental also varied in the same manner.
2. Premedication varied. The protocol called for meperidine 1 mg/kg. In actual practice, the dose of meperidine varied from 0.63-1.58 mg/kg. The dose of atropine also varied more than specified in the protocol.
3. The investigator did not always follow the randomized code.

No unusual safety problems were revealed by this study:

Protocol 2127A:

Philip Lebowitz, M.D., Massachusetts General Hospital, Boston.

The intent was to compare midazolam and thiopental in patients who required repeated anesthesia. Seven patients participated, 4 for midazolam and 3 for thiopental. As it turned out, all of the midazolam patients turned out to require anesthesia only once. The study was abandoned because of lack of suitable patient material. No conclusions can be reached.

SAFETY: For all practical purposes, there were no safety problems.

Protocol 2160:

Philip Lebowitz, M.D., as above.

The objective was to study renal function after midazolam hydrochloride induction and after thiopental sodium induction in good risk patients, free of renal disease, who none-the-less required urinary bladder catheterization for surgery. Eight midazolam patients and 9 thiopental patients participated. There were multiple sampling problems, laboratory problems (including lost results), etc. which finally led to abandoning the rest of the study. No conclusions about renal function can be reached because of lack of samples for calculations, etc.

SAFETY: The only unusual observation was transient burning on injection in one midazolam patient, judged possibly drug related.

11-2

VERSED

18654

000105

Comparable levels of sedation were attained with mean doses of 0.095 mg/kg of midazolam and 0.180 mg/kg of diazepam. Midazolam patients required a significantly shorter mean time to reach the sedative end point of slurred speech than did diazepam-treated patients (4.3 vs. 6.1 minutes).

The sedative and impairment of recall properties of midazolam and diazepam were similar as rated by the physicians and the patients. In both assessments the sedative properties were rated "good" or "excellent". Both drugs produced impairment recall of the procedure. Psychomotor recovery was similar for the two groups.

Transient comparable fluctuations in vital signs occurred in both groups. Hypotension noted in one midazolam-treated patient was attributed to meperidine. Several patients in one study had prolonged drowsiness and this occurred in both drug groups. This effect was attributed to the combined effects of 1 mg/kg of meperidine administered concomitantly with the sedative agent.

The results of this study showed that midazolam, when used with meperidine and a topical anesthetic agent, is as safe and effective as diazepam in inducing sedation and producing diminished recall of the procedure. Doses of both meperidine and the benzodiazepines should have been reduced to prevent oversedation of some patients.

000106

Study No. 102

Title: A Comparison of Midazolam and Diazepam in Combination With Meperidine During Local Anesthesia for Gastroscopy

Investigator: Paul F. White, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in 21 adults undergoing gastroscopy for the first time.

Subjects

Twenty-one patients (ASA I or II) undergoing diagnostic gastroscopy for the first time. The study population was comprised of 5 non-pregnant females and 16 males ranging in age from 22 to 73 years. In the midazolam group there were 8 males and 3 females with a mean age of 55.3 years (range 22-69). In the diazepam group there were 8 males and 2 females with a mean age of 56.9 years (range 28-73).

Study Drugs: See Study 104

Experimental Design: See Study 104

Results

Deviations from Protocol

Two patients in the midazolam group were excluded from all efficacy analyses. Patient was excluded because morphine, which was an excludable concomitant medication, was administered prior to the procedure to alleviate severe abdominal pain resulting from a pancreatic pseudocyst. Patient required the administration of a narcotic antagonist to reverse meperidine-induced hypotension.

Induction of Intravenous Sedation

Comparable levels of intravenous sedation were achieved with mean doses of 0.091 mg/kg of midazolam and 0.187 mg/kg diazepam. An additional dose to maintain sedation was required by one patient in each treatment group. The mean time to reach the sedative end point and the duration of the procedures were similar for both groups.

000107

Physician's Assessment

The physician's assessment of sedation was in most instances "good" to "excellent" for both midazolam and diazepam-treated patients. There were no significant differences between treatments in the physician's assessment of sedation.

Patient's Assessment

One hour after the procedure all but one midazolam patient rated the sedation produced by each drug as "good" or "excellent" and reported little or no pain associated with the gastroscopy. On the following day, one midazolam patient rated sedation as fair and also felt that the gastroscopy was very painful. All patients indicated, one hour after the procedure, that they would elect to undergo the procedure the same way again. On the following day, one midazolam patient changed his response.

Trieger Test

There were no significant differences between the two groups in psychomotor recovery from sedation. There was an increase in the number of dots missed and total deviation from the dots compared with the baseline in both groups one hour after the procedure with return toward the baseline values at two hours.

Follow-Up Questionnaire for Amnesia

Most patients could recall events prior to sedative administration. Failure of recall of scope introduction and withdrawal was induced in all but 1 midazolam and in 2 diazepam patients at one hour after the procedure and in all but 3 midazolam and 1 diazepam patients on the following day.

Safety

On returning 11 days after gastroscopy for the follow-up examination, a 69 year-old male patient (midazolam) with a previous history of myocardial infarction, reported experiencing severe chest pains for several weeks. An electrocardiogram revealed an anterior myocardial infarction of undetermined age. The investigator felt that this event was remotely related to the test drug.

A 66 year-old male, who received 0.100 mg/kg of midazolam, experienced hypotension at the end of the procedure. This was reversed with 0.4 mg of Narcan and was attributed to the administration of meperidine.

000106

Two midazolam-treated patients (.045 mg/kg and 0.1 mg/kg) and three diazepam-treated patients experienced an extended period of drowsiness following the completion of the study and were required to remain at the study center for an additional period (up to 100 minutes). In this study, the investigator administered 1 mg/kg of meperidine to all patients.

Two patients who received midazolam had evidence of venous irritation on the follow-up examination.

Most changes in vital signs were transient and were most often associated with the gastroscopy. Changes were usually mild to moderate with severe changes only occurring for an increase in pulse rate. One midazolam-treated patient had a severe increase in pulse rate during maintenance, and patient who received diazepam, had a severe increase in pulse rate both during induction and maintenance.

Summary and Conclusions

This randomized, double-blind study compared the use of I.V. midazolam and I.V. diazepam as adjuncts to intramuscular meperidine and local anesthetic administration for the production of sedation for gastroscopy. Both agents were effective. Assessments of sedation by both the physician and patients were in most instances "good" to "excellent". All patients after one hour indicated that they would elect to undergo the procedure the same way again and only 1 midazolam patient changed his opinion on the following day.

Recovery from sedation showed similar patterns in both groups. Impairment of recall of the gastroscopy was induced in most patients in both groups.

A remotely related to midazolam myocardial infarction was detected on follow-up examination as were three cases of venous irritation. There were two in midazolam patients and one in a diazepam patient.

Hypotension was noted in one midazolam patient and was attributed to meperidine. Several patients in both groups experienced extended periods of drowsiness which may have been related to a 1 mg/kg dose of meperidine administered with the benzodiazepine.

000109

Study No. 104

Title: A Comparison of Midazolam and Diazepam in Combination with Meperidine During Local Anesthesia for Gastroscopy

Investigator: John F. Horrissey, M.D.

Objective:

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in 20 adults undergoing gastroscopy for the first time.

Subjects

Twenty patients (ASA I or II) undergoing diagnostic gastroscopy for the first time. The study population was comprised of 10 non-pregnant females and 10 males ranging in age from 20 to 76 years. In the midazolam group there were 2 males and 8 females with a mean age of 45.2 years (range 20-76). In the diazepam group there were 8 males and 2 females with a mean age of 46.4 years (range 21-65).

Study Drugs

Approximately 30 minutes before the gastroscopy, meperidine 50-75 mg and atropine 0.5 mg were administered intramuscularly. Following topical anesthetic administration, 5.0-7.5 mg of either midazolam or diazepam were administered intravenously over a 2-3 minute period. Elderly patients received 2.50-3.75 mg of the test medications over the same time interval. Incremental doses (25% of initial dose) were administered, if necessary, until the patient's speech became thickened and slurred but the patient was still responsive to verbal commands.

Experimental Design

Immediately following the gastroscopy, the blinded physician evaluated as excellent, good, fair or poor the sedative effects produced by the test medication. The assessments included (1) patient cooperation, (2) muscle relaxation, (3) ease of endoscopic examination, (4) control of gag reflex, (5) control of laryngospasm, (6) control of cough reflex, (7) control of retching and vomiting, (8) control of salivation and (9) overall tolerance of the procedure. One hour after gastroscopy and one day later in a follow-up questionnaire, patients evaluated the sedation during the procedure as excellent, good, fair or poor. In addition on both occasions, patients were asked if they would elect to undergo a future gastroscopy the same way, if necessary. One hour after gastroscopy patients evaluated the procedure as not painful, somewhat painful or very painful and whether they could recall none, some or all of the gastroscopy. In the follow-up questionnaire, patients were also asked whether they could recall clearly, vaguely or not at all events before, during and after gastroscopy.

000110

Recovery from sedation was assessed by the Trieger Test which was completed by the patient before medication (baseline) and at 60 and 120 minutes following the completion of the gastroscopy. Each Trieger Test was evaluated for the number of dots missed and the total deviation (mm) from the dots.

Vital signs were monitored before, during and after gastroscopy. Changes in vital signs greater than 20% from baseline were identified as possible adverse experiences. The severity of the changes was categorized as:

mild - a change $\geq$ 20 percent out $<$ 30 percent from baseline
moderate - a change $\geq$ 30 percent but $<$ 50 percent from baseline
severe - a change $\geq$ 50 percent from baseline or treatment required

Adverse experiences were further categorized according to the phase of the study as induction, maintenance (gastroscopy) and recovery. Seven to 14 days following the study the intravenous injection site was examined for tenderness, redness and induration.

Results

Induction of Intravenous Sedation

Comparable levels of sedation were achieved with mean doses of 0.10 mg/kg of midazolam and 0.173 mg/kg of diazepam. Midazolam-treated patients required a significantly shorter mean time to reach the sedative end point than diazepam-treated patients (3.65 vs. 6.67 minutes).

Physician's Assessment

In most instances the assessment of sedation was "good" to "excellent" for both groups of patients. There were no significant differences between treatments.

Patient's Assessment

On both evaluation occasions (one hour after the procedure and the following day), all patients rated the sedation produced by midazolam or diazepam as "good" to "excellent." One hour after the procedure 9 of 10 midazolam patients and all of the diazepam patients responded that they would elect to undergo the procedure the same way again. By the following day this response was unanimous. Both test groups indicated that there was little or no pain associated with the gastroscopy.

Trieger Test

There were no statistically significant differences between groups in recovery from sedation. More dots were missed by the midazolam group one hour following the gastroscopy than by the diazepam group. This was true for total deviation from the dots as well. By two hours the results were returning to near baseline value.

000111

Follow-up Questionnaire for Amnesia

The responses of one diazepam-treated patient to recall the one and two hour Trieger Tests were not analyzed. This patient remembered doing the Trieger Test only once after the procedure but did not know whether it was the one or two hour test. All patients recalled the procedures prior to being sedated. Lack of recall of the scope introduction and withdrawal was induced in all midazolam and most diazepam patients. This period was extended to one hour in half of the midazolam-treated patients, while the majority of the diazepam patients recalled their one hour Trieger Test.

Safety

Adverse experiences were limited to vital sign changes and venous irritation. Most changes in vital signs were transient and were most often associated with the gastroscopy. Several midazolam-treated patients had severe increases in pulse rate, while several diazepam-treated patients had severe increases in both respiration and pulse rate.

Patient who received midazolam, had evidence of venous irritation for one week following the procedure. The injection site showed signs of tenderness, redness and induration. Patient who received diazepam, also had tenderness and induration at the injection site on the follow-up examination.

Summary and Conclusions

- This randomized, double-blind study compared the use of IV midazolam and IV diazepam as adjuncts to intramuscular meperidine and local anesthetic administration for the production of sedation for gastroscopy. Both agents were effective. Assessments of sedation by both the physician and the patients were "good" to "excellent" in most instances. By the following day, all patients indicated they would elect to undergo the procedure the same way again.

Midazolam-treated patients had less recall of events during and following the gastroscopy than did patients in the diazepam group. Midazolam patients had more impairment of psychomotor performance one hour following the procedure than diazepam patients, although the difference was not statistically significant. Changes in vital signs were not clinically significant. Venous irritation was noted in one patient from each treatment group.

This study showed that midazolam, when used in combination with meperidine and a topical anesthetic agent, is as safe and effective as diazepam in inducing sedation for gastroscopy. Midazolam may have been a better agent for the induction of impaired recall of operative and post-operative events.

Study No. 109, Protocol 2241A

Title: A Comparison of Midazolam and Diazepam as Intravenous Sedation for Elective, Direct-Current Cardioversion

Investigator: Tennyson G. Lee, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in patients undergoing elective, direct-current cardioversion for supraventricular tachyarrhythmias.

Subjects

There were only five subjects entered into the study at the time of submission. There was one midazolam-treated patient, age 30. There were four diazepam-treated patients aged 57-81.

Study Drugs

The investigator titrated slowly the initial and incremental doses of either midazolam or diazepam (5-15 mg) until the patient's speech became slurred and thickened but the patient was still responsive to verbal commands. In addition, 1-5 mg of test medication was administered if the investigator felt that the patients required more sedation prior to electrocardioversion.

Experimental Design

This was a randomized, double-blind, parallel group study. The initial and subsequent countershock energy levels were determined by the investigator. The drug dose and time required to induce sedation were calculated. The drug effects were assessed by both the physician and the patient. Immediately following the cardioversion, the physician evaluated (a) quality of sedation, (b) patient's cooperation, (c) muscle relaxation, and (d) patient's overall tolerance of the procedure. One hour after cardioversion and one day later in a follow-up questionnaire, patients evaluated (a) quality of sedation, (b) pain during the procedure, (c) memory of the procedure, and (d) whether they would elect to undergo a future cardioversion, if necessary, the same way.

Recovery from sedation was assessed by the Trieger Test which was completed by the patient before medication (baseline) and at 60 and 120 minutes following the completion of cardioversion. Each Trieger Test was evaluated for the number of dots missed and the total deviation (mm) from the dots.

Continuous electrocardiographic monitoring was done before, during and after completion of the procedure while the patient was in the procedure or recovery room. Blood pressure, respiratory rate and pulse rate were monitored before, during and after cardioversion. Significant changes in vital signs from baseline, were identified as possible adverse experiences (mild: $\geq 20\%$ but $< 30\%$ change; moderate $\geq 30\%$ but $< 50\%$ change; and severe $\geq 50\%$ change from baseline). The intravenous injection site was examined 7-14 days following the procedure for possible venous irritation.

Results

Drug Dose and Time Required to Induce Sedation

The one midazolam patient received 0.136 mg/kg to induce sedation and induction time was 3 minutes. The four diazepam patients received from 0.064 mg to 0.122 mg/kg to induce sedation and induction time was 2 to 5.93 minutes.

Physician's Assessment

The midazolam patient rated "excellent" to "good" on all parameters. Midazolam treatment was rated "excellent" on about half the parameters in each case and "poor" to "good" on the others with no pattern developing.

Patient's Assessment

The quality of sedation was rated as "excellent" by all five patients. Twenty-four hours after cardioversion, none of the five patients had any recall of the procedure and at one hour only one diazepam patient had any recall.

Trieger Test

Two diazepam patients missed more dots on both tests after cardioversion and had more deviation than at the baseline measurement. Midazolam patient missed more dots and had more deviation on the one hour test, but, at two hours, he missed fewer dots than on the baseline measurement.

Safety

Patient who received midazolam had transient apnea with spontaneous improvement. Cardioversion was carried out with no problems. A similar apnea problem was observed in patient who received diazepam. Respiratory rate, pulse rate and mean arterial pressure fluctuated more than 20% from baseline intermittently; however, these changes were transient and clinically insignificant. There was no venous irritation or phlebitis.

Summary and Conclusions

No comparisons are possible since only one midazolam and four diazepam patients were included in this study. There was one incidence of transient apnea in each study group.

Pooled Study Summary
Study Nos. 114, 115, 122, Protocol 2242A

Title: A Comparison of Midazolam and Diazepam With Meperidine Pretreatment for Sedation During Cardiac Catheterization

Subjects

Sixty two patients (ASA I, II or III) undergoing diagnostic cardiac catheterization for the first time participated in the study. The study population consisted of 21 non-pregnant females and 41 males ranging in age from 31 to 68 years. In the midazolam group there were 30 patients comprised of 18 males and 12 females with a mean age of 53.8 years (range 31-68). In the diazepam group there were 32 patients comprised of 23 males and 9 females with a mean age of 51.1 years (range 36-64).

Results

Differences Among Study Centers

The doses of meperidine and of the test medications varied among the three centers. The patients in Study 115 received a relatively higher dose of meperidine; consequently they required lesser amounts of the test medications and a shorter time to induce sedation than the patients in the other two centers.

Deviations from Protocol

These are addressed in the individual study summaries.

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean initial doses of 0.072 mg/kg IV midazolam and 0.092 mg/kg IV diazepam, in respective mean induction times of 4.83 minutes and 8.95 minutes. The midazolam-treated patients required a significantly shorter time and less test drug to attain the sedative end point than the diazepam group.

Physician's Assessment

The mean scores for quality of sedation, muscle relaxation and overall patient tolerance among the midazolam-treated patients were significantly higher than among the diazepam-treated patients.

Patient's Assessment

One hour after the procedure 13 of 30 midazolam patients had complete recollection of the procedure compared with 26 of 30 diazepam patients.

Twenty four hours after the procedure, only 9 of 30 midazolam patients had complete recollection of the procedure compared with 24 of 30 patients in the diazepam group. One hour after the procedure, a greater number of midazolam patients rated the quality of sedation as "excellent" than those in the diazepam group (24 vs. 18). The majority of patients in each group had either no pain or minimal pain during the procedure and would elect to have a future procedure conducted the same way.

Trieger Test

The results of the two groups were comparable at one and two hours following catheterization and the pattern of recovery from sedation was similar for both groups.

Adverse Reactions

Table 1

Clinical Adverse Experiences

	<u>Midazolam (n=30)</u>		<u>Diazepam (n=32)</u>	
	<u># pts.</u>	<u>Percent</u>	<u># pts.</u>	<u>Percent</u>
<u>Possibly and Probably Related Drug Effects</u>				
<u>Respiratory System</u>				
Respiration Rate Increase	10	33.3	14	43.8
Respiration Rate Decrease	12	40.0	11	34.4
<u>Cardiovascular System</u>				
Pulse Increase	14	46.7	10	31.3
Pulse Decrease	7	23.3	6	18.8
MAP Decrease	16	53.3	8	25.0
MAP Increase	0	0	1	3.1
<u>Gastrointestinal</u>				
Acid Taste	1	3.3	0	0
Nausea	1	3.3	0	0
Vomiting	1	3.3	0	0
<u>Central Nervous</u>				
Headache	1	3.3	0	0
<u>Remotely Related Drug Effect</u>				
<u>Cardiovascular</u>				
Asystole	0	0	1	3.1
Tenderness of Vein	0	0	1	3.1
<u>Gastrointestinal</u>				
Nausea	1	3.3	2	6.3
Vomiting	0	0	2	6.3

None of the cardiovascular or respiratory adverse experiences were clinically significant and none required any specific corrective measures. Patients were examined 7-14 days following catheterization and none of the midazolam-treated patients had any clinical evidence of vein irritation or phlebitis at the intravenous injection site.

Summary and Conclusions

In this multicenter study the results of three randomized, double-blind parallel group studies included 62 adults. It was demonstrated that both midazolam and diazepam were effective intravenous sedative agents for cardiac catheterization when used in patients premedicated with meperidine. Comparable levels of sedation (slurred speech) were attained with initial mean doses of 0.072 mg/kg of IV midazolam and 0.092 mg/kg of IV diazepam. The mean time required to attain the sedative end point was 4.83 minutes for midazolam and 8.95 minutes for diazepam.

The physician's assessment showed that the midazolam-treated patients were significantly more relaxed, more sedated and had better tolerance of the procedure than the diazepam group. The patient's assessment revealed some superiority of midazolam over diazepam with respect to the quality of sedation. A greater number of midazolam patients had impaired recall of the procedure.

The pattern of psychomotor recovery was similar for both groups. Vital sign fluctuations occurred transiently during catheterization; however, these changes were clinically insignificant and required no corrective measures. Other adverse experiences were of minor nature and infrequent.

This study demonstrated that IV midazolam when used with meperidine as premedicant in cardiac catheterization is as safe as diazepam. It has some superiority in diminishing recall of the procedure and appears to have an earlier onset of action. In the doses employed it effectively provided sedation.

Study No. 114

Title: A Comparison of Midazolam and Diazepam With Meperidine Pretreatment for Sedation During Cardiac Catheterization

Investigator: Goffredo G. Gensini, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam when given in conjunction with meperidine as a premedication, for sedation during cardiac catheterization.

Experimental Design

Randomized, double-blind parallel study in 22 adults undergoing diagnostic cardiac catheterization for the first time. Prior to catheterization midazolam or diazepam was administered by random coded assignment. Immediately following the catheterization, the physician evaluated (a) quality of sedation, (b) patient's cooperation, (c) muscle relaxation, and (d) patient's overall tolerance of procedure. One hour after catheterization and one day later in a follow-up questionnaire, patients evaluated (a) quality of sedation, (b) pain during the procedure, (c) memory of the procedure, and (d) whether they would elect to undergo a future catheterization, if necessary, the same way.

Recovery from sedation was assessed by the Trieger Test which was completed by the patient before medication (baseline) and at 60 and 120 minutes following the completion of catheterization. Each Trieger Test was evaluated for the number of dots missed and the total deviation (mm) from the dots.

Continuous electrocardiograph monitoring was done before, during and after completion of the procedure while the patient was in the catheterization laboratory. Blood pressure, respiratory rate and pulse rate were monitored before, during and after catheterization. Changes in vital signs greater than 20% from baseline were identified as possible adverse experiences. The intravenous injection site was examined 7-14 days following the procedure for possible venous irritation.

Subjects

There were 4 non-pregnant females and 18 males, ranging in age from 36 to 64 years (ASA Class I-III). In the midazolam group there were 10 males and 0 females with a mean age of 56.8 years (range 64-103). In the diazepam group there were 8 males and 4 females with a mean age of 50.7 years (range 36-64).

Study Drugs

Approximately 30 minutes before catheterization, all patients (except patient - diazepam group) received meperidine 25 mg IM. Patient was excluded from efficacy analyses for procedural complications. Based on the patient's age and clinical condition, the investigator slowly administered (2-3 minutes) the initial and incremental doses (1-10 mg) of either midazolam or diazepam until the patient's speech became slurred and thickened but the patient was still responsive to verbal commands. In addition, 1-5 mg of test medication was administered, if necessary, to maintain adequate sedation during cardiac catheterization.

Results

Deviations from Protocol

Patient - diazepam. Investigator decided to deviate from the protocol, due to his lack of experience with test drug, after administration of 7.5 mg of test medication to the patient. Additional test drug was not given and sedation was not induced as directed in the protocol.

Patient - diazepam. During cardiac catheterization, immediately following ventriculography, patient's electrocardiogram showed ST-segment elevation, progressing to asystole. Investigator felt this to be related to injection of contract agent used for ventriculography. Patient responded to treatment. Nonetheless, investigator decided to terminate subsequent study procedure.

Patient - diazepam. Could not complete the 2-hour post-catheterization Trieger Test due to nausea and vomiting.

Induction of Intravenous Sedation

Midazolam-treated patients required a mean initial dose of 0.067 mg/kg (range 0.049-0.078) compared to 0.110 mg/kg (range 0.063-0.155) required by the diazepam group. None of the patients required any additional medication to maintain sedation during catheterization. The mean induction time was 7.2 minutes with midazolam and 16.19 minutes with diazepam. The midazolam time was significantly faster.

Physician's Assessment

The quality of sedation, muscle relaxation and patient's overall tolerance in midazolam-treated patients were rated as "excellent" by the physician who performed the catheterization. These ratings were significantly better than those in the diazepam group, rated "fair" to "good."

Patient's Assessment

One hour after completion of the catheterization, only 40% (4 of 10) and on the following day, only 30% (3 of 10) of the midazolam-treated patients could recall the procedure completely, compared with a complete recollection by all patients (10) in the diazepam group. All midazolam patients were pain-free during the procedure, while 3 of 10 diazepam patients experienced some pain. Nine midazolam-treated patients rated the quality of sedation as "good" to "excellent" compared with 7 diazepam patients. In each treatment group all of the patients would elect to undergo a future procedure the same way on the one hour rating. After one day one patient changed this opinion in each group.

Trieger Test

Although the sponsor indicated similar patterns of recovery from sedation for both groups this reviewer disagrees. The midazolam-treated group had greater changes from baseline after one hour, and returned toward baseline at two hours. The diazepam-treated group progressively deteriorated away from the baseline from one to two hours post-catheterization.

Adverse Reactions

Table 1

Clinical Adverse Experiences

	<u>Midazolam</u>		<u>Diazepam</u>	
	<u># pts.</u>	<u>Percent</u>	<u># pts.</u>	<u>Percent</u>
<u>Possibly and Probably Related Drug Effects</u>				
<u>Respiratory System</u>				
Respiratory Rate Increase	1	10	8	66.7
Respiratory Rate Decrease	7	70	7	58.3
<u>Cardiovascular System</u>				
Pulse Increase	4	40	4	33.3
Pulse Decrease	4	40	2	16.7
MAP Decrease	8	80	4	33.3
<u>Gastrointestinal</u>				
Acid Taste	1	10	0	0
Nausea	1	10	0	0
Vomiting	1	10	0	0
<u>Central Nervous</u>				
Headache	1	10	0	0
<u>Relationship to Test Drug - Remote</u>				
<u>Cardiovascular</u>				
Asystole	0	0	1	8.3
Tenderness of Vein	0	0	1	8.3
<u>Gastrointestinal</u>				
Nausea	0	0	1	8.3
Vomiting	0	0	1	8.3

The majority of changes from baseline in vital signs were transient and clinically insignificant. None of the midazolam-treated patients experienced any clinically significant respiratory or cardiovascular problems.

Summary and Conclusions

This randomized, double-blind study compared the use of midazolam with diazepam to provide sedation during cardiac catheterization in patients premedicated with meperidine. Midazolam provided "excellent" sedation and was felt by physician and patient to be a superior sedative agent when compared to

diazepam. Recall of the procedure was considerably less in the midazolam-treated group. The mean initial sedative dose of 0.067 mg/kg of IV midazolam and 0.1110 mg/kg of IV diazepam induced adequate sedation in patients premedicated with meperidine. The mean time required to attain slurred speech was 7.2 minutes for the midazolam-treated patients and 16.19 minutes for the diazepam group. The pattern of recovery from sedative effects, as assessed by the Trieger Test showed more progress toward the baseline condition in the midazolam group.

None of the midazolam-treated patients had any clinically significant complications. There were infrequent transient complaints such as nausea, vomiting, headache and "acid-taste." There were no clinically significant cardiovascular or respiratory problems. The results of this study showed that IV midazolam was safe when used to provide sedation during cardiac catheterization in patients premedicated with meperidine and appeared to be superior to IV diazepam with respect to sedation and diminished recall of the procedure.

Study No. 115

Title: A Comparison of Midazolam and Diazepam With Meperidine Pretreatment for Sedation During Cardiac Catheterization

Investigator: Grady G. Hendrix, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam given in conjunction with meperidine as a premedication for sedation during cardiac catheterization.

Experimental Design

Randomized, double-blind parallel study in 20 adults undergoing diagnostic cardiac catheterization for the first time. The design of this study was similar to that of study 114 since this was a multicenter study following the same protocol.

Subjects

There were 11 non-pregnant females and 9 males, ranging in age from 38 to 67 years (ASA Class I-III). In the midazolam group there were 2 males and 8 females with a mean age of 54.6 years (range 43-67). In the diazepam group there were 7 males and 3 females with a mean age of 51.5 years (range 38-61).

Study Drugs: See Study 114.

ResultsDeviations from Protocol

Although the doses of the test drug were specified in the protocol, the investigator adjusted the doses of the initial and subsequent test-drug injections according to the patient's age, weight and overall clinical conditions.

All patients were included in the analyses; however, Trieger Test results of three patients were excluded.

Patient _____ - midazolam. Baseline Trieger Test was not done prior to the test-drug injection as directed in the protocol.

_____ midazolam. Due to incision in right arm, patient could not do post-catheterization Trieger Tests. Only baseline Trieger Test was available.

_____ - diazepam. Same as patient

- midazolam. Could not complete the two-hour post-catheterization Trieger Test due to nausea, the baseline and one-hour post-catheterization results of this patient were analyzed. This patient received 25 mg PO thioridazine approximately 18 hours prior to the test drug administration. It was decided to include the patient in all analyses since she was taking the drug chronically on a daily basis and her case record did not reveal any unusual pattern of results.

Induction of Intravenous Sedation

Midazolam-treated patients required a mean initial dose of 0.051 mg/kg (range 0.028-0.097) to reach the sedative end point compared to 0.057 mg/kg (range 0.017-0.115) required by the diazepam group. Midazolam patients required an additional mean dose of 0.010 mg/kg (range 0-0.040) to maintain adequate sedation during catheterization compared with 0.018 mg/kg (range 0-0.047) required by diazepam-treated patients. The mean total dose for midazolam group was 0.061 mg/kg (range 0.028-0.097) compared with 0.075 mg/kg (range 0.017-0.155) for diazepam. The mean induction time was 2.1 minutes with midazolam and 2.7 minutes with diazepam.

Physician's Assessment

The quality of sedation, muscle relaxation, patient's cooperation and patient's overall tolerance for both midazolam and diazepam groups were rated as "good" to "excellent" by the physician who performed the catheterization.

Patient's Assessment

One hour after completion of catheterization, a greater number of midazolam-treated patients experienced no recall of the procedure than the diazepam group, with only 5 of 10 midazolam patients compared with all 10 diazepam patients having a complete recollection of the procedure. In both groups patients experienced either no pain at all or minimal pain. The quality of sedation was rated as "good" to "excellent" by both groups, with 1 patient in each group giving a "fair" rating. Eight of ten of the midazolam and nine of ten diazepam-treated patients would undergo the procedure the same way again.

Trieger Test

The pattern of recovery from sedation was similar for both groups of patients.

Adverse Reactions

Respiratory rate decreased in 20% of the midazolam-treated and 10% of the diazepam-treated patients; however, during the same period, respiratory rate increased in 20% of the patients in each group. Most of these changes were mild, transient and clinically insignificant and none of the patients required any specific corrective measures. Minor transient fluctuations in blood pressure and pulse rate were noted during catheterization--these changes are not uncommon during cardiac catheterization.

- in the midazolam group had transient nausea approximately two hours after completion of catheterization which, according to the investigator was not related to the test drug. No other adverse reactions were noted. Patients were examined 7-14 days following catheterization and no patient had clinical evidence of vein irritation or phlebitis at the intravenous injection site.

Summary and Conclusions

This randomized double-blind study compared the use of midazolam with diazepam to provide sedation during cardiac catheterization in patients premedicated with meperidine. Midazolam and diazepam both provided "good" to "excellent" sedation in the majority of patients during cardiac catheterization. The mean initial sedation doses were comparable and induced adequate sedation. The initial dose was 0.057 mg/kg of IV diazepam and 0.051 mg/kg of IV midazolam. The mean induction time was 2.7 minutes and 2.1 minutes respectively. One hour after completion of cardiac catheterization, midazolam patients had less recall of the procedure than the diazepam group. Patterns of psychomotor recovery were similar for both groups.

There were no significant adverse reactions in this study. The results of this study showed that IV midazolam was safe when used to provide sedation during cardiac catheterization in patients premedicated with meperidine and was as effective as IV diazepam while providing for less recall of the procedure in some cases.

Study No. 122

Title: A Comparison of Midazolam and Diazepam With Meperidine Pretreatment for Sedation During Cardiac Catheterization

Investigator: Philip A. Ludbrook, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam given in conjunction with meperidine as a premedication for sedation during cardiac catheterization.

Experimental Design

Randomized, double-blind parallel study in 20 adults undergoing diagnostic cardiac catheterization for the first time. The design of this study was similar to that of study 114 since this was a multicenter study following the same protocol.

Subjects

There were 6 non-pregnant females and 14 males, ranging in age from 31 to 68 years (ASA Class I-III). In the midazolam group there were 6 males and 4 females with a mean age of 50.1 years (range 31-68). In the diazepam group there were 8 males and 2 females with a mean age of 51.1 years (range 42-59).

Study Drugs: See Study 114.

ResultsDeviations from Protocol

Although the doses of meperidine and the test drug were specified in the protocol, the investigator adjusted the doses of these medications according to the patient's age, weight and overall clinical status. Otherwise, there were no significant deviations from the protocol. All patients were included in all analyses.

Induction of Intravenous Sedation

Midazolam-treated patients required a mean initial dose of 0.097 mg/kg (range 0.075-0.112) to reach the sedative end point compared to 0.110 mg/kg (range 0.079-0.197) required by the diazepam group. Midazolam-treated patients required an additional dose of 0-0.083 mg/kg to maintain adequate sedation during catheterization compared with 0.013-0.080 mg/kg required by diazepam-treated patients. The mean total dose for midazolam patients was 0.124 mg/kg compared with 0.142 mg/kg for diazepam. The mean time required to attain the sedative end point was 5.2 minutes for the midazolam patients and 8.0 minutes for the diazepam group.

Physician's Assessment

Midazolam-treated patients had significantly higher scores than the diazepam-treated group with respect to quality of sedation and patient tolerance. The quality of sedation, muscle relaxation, patient's cooperation and patient's overall tolerance were rated as "excellent" for the majority of midazolam patients. The corresponding ratings were "good" to "excellent" for the diazepam group.

Patient's Assessment

At 24 hours after catheterization, a greater number of midazolam-treated patients experienced less recall of the procedure than the diazepam group; however, this difference was not seen at the one-hour post-catheterization evaluation. In both groups minimal or no pain was experienced and the quality of sedation was rated as "good" to "excellent." All patients would have the procedure performed the same way again.

Trieger Test

The pattern of recovery from sedation was similar for patients in both groups.

Adverse Reactions

Changes in vital signs were transient and clinically insignificant. None of the patients required any corrective measures. There were no significant differences between the two groups. None of the patients had any clinically significant respiratory depression or hypotension.

Patient - diazepam had transient nausea and vomiting following catheterization and, according to the investigator this was related to the contract media utilized during catheterization. No other adverse reactions were noted. Patients were examined 7-14 days following catheterization and no patient had clinical evidence of vein irritation or phlebitis at the intravenous injection site.

Summary and Conclusions

This randomized, double-blind study compared the use of midazolam with diazepam to provide sedation during cardiac catheterization in patients premedicated with meperidine. A mean initial sedation dose of 0.097 mg/kg of IV midazolam and 0.110 mg/kg of IV diazepam induced adequate sedation in mean times of 5.2 and 8 minutes, respectively. The physician's assessment revealed that midazolam-treated patients were significantly more sedated and had better tolerance of the procedure than the diazepam group.

In both groups, the patients rated the quality of sedation as "good" to "excellent." Twenty four hours after catheterization, a greater number of midazolam-treated patients experienced partial or no recall of the procedure than in the diazepam group.

There were no significant adverse experiences in this study. These transient fluctuations in vital signs, but these were clinically insignificant and did not require any corrective measures. The results of this study showed that IV midazolam was safe when used to provide sedation during cardiac catheterization in patients premedicated with meperidine and was as effective as IV diazepam while providing for less recall of the procedure in some cases.

Study No. 009, Protocol 1032

Title: Comparison Between Diazepam and Midazolam of Cardiovascular and Sedative Effects during Cardiac Catheterization

Investigator: Robert J. Fragen, M.D.

Objective

This study was designed to compare the cardiovascular effects of intravenous midazolam with diazepam and saline in patients undergoing cardiac catheterization for suspected coronary artery disease.

Experimental Design

Randomized, double-blind parallel study in thirty adults undergoing cardiac catheterization. Patients had stable angina pectoris and were unpremedicated. They were randomly assigned to three groups: 10 midazolam, 10 diazepam and 10 normal saline. A Swan-Ganz thermodilution catheter was inserted to measure pulmonary capillary wedge pressure, right atrial pressure and cardiac output. A catheter was inserted to measure aortic pressure. Cardiac index, systemic vascular resistance and left ventricular stroke work index were calculated using standard formulae.

Degree of sedation was assessed on a 4-point scale: 0 = none, 1 = mild, 2 = moderate, 3 = marked. Bolus injections of midazolam 0.05 mg/kg, diazepam 0.10 mg/kg or saline 0.02 ml/kg were administered intravenously. All hemodynamic measurements were made under baseline, control pre-treatment conditions and at 5 and 15 minutes after test drug injection. Respiration rate was also recorded at baseline and 5 and 15 minutes after injection. Changes in vital signs were evaluated according to the following criteria.

Mild = $\geq 20\%$ but $< 30\%$ change from control

Moderate = $\geq 30\%$ but $< 50\%$ change from control

Severe = $\geq 50\%$ change from control

Subjects

There were 30 patients ranging in age from 35 to 66. In the midazolam group there were 7 males and 3 females with a mean age of 50.4 (range 35-62). In the diazepam group there were 8 males and 3 females with a mean age of 56.4 (range 48-66). In the saline group there were 10 males and no females with a mean age of 48.7 (range 35-59).

Study Drugs

There were three groups of patients: Each group consisted of 10 patients. Bolus injections of either diazepam 0.10 mg/kg, midazolam 0.05 mg/kg or saline 0.02 ml/kg were administered by an intravenous injection into a free running IV fluid line over one minute. The contents of the injection were unknown to the patient and the catheterization team.

Results

Deviations from Protocol

The investigator utilized a randomized code generated at his institution rather than that supplied by the sponsor.

Hemodynamic Parameters

1. Left ventricular function:

There were no significant differences between midazolam and diazepam in parameters of left ventricular function (cardiac output, cardiac index, stroke index, stroke volume, left ventricular stroke work index). Significantly greater decreases were observed with midazolam than saline in stroke volume at 5 minutes and 15 minutes and in left ventricular stroke work index at 15 minutes; however, these were not major alterations.

2. Vital signs: With respect to vital signs, there was a greater decrease in systolic blood pressure with midazolam than saline at 15 minutes; however, no changes in vital signs were significantly different between groups. In only one instance did the change from baseline exceed 20% (increased mean arterial pressure in one diazepam-treated patient).

3. Pressures (pulmonary arterial systolic, pulmonary arterial diastolic, mean pulmonary artery, pulmonary capillary wedge and right atrial pressure): The only change to reach significance was a greater decrease in pulmonary capillary wedge pressure, at 15 minutes with midazolam than saline, but this was of small magnitude. There were no significant differences between midazolam and diazepam.

4. Resistance (total systemic, total pulmonary, pulmonary arteriolar resistances): No significant differences between midazolam and diazepam were noted.

5. Arterial blood gases (O_2 , pH, pO_2 , pCO_2 , O_2 saturation, HCO_3 , base excess) and venous blood gases (pH, pO_2 , pCO_2 , O_2 content, venous HCO_3 , base excess, O_2 saturation): There were isolated differences between midazolam and diazepam and between midazolam and saline; however, there was no consistent trend nor any clinically significant effect.

6. Sedation: At five and fifteen minutes patients who received midazolam or diazepam were more sedated than those who received saline, and midazolam patients were significantly more sedated than were diazepam patients. Following injection approximately half the diazepam-treated patients were mildly sedated at 5 and 15 minutes, while only one saline-treated patient was mildly sedated. With midazolam, 8 out of 10 patients were mildly or moderately sedated at 5 and 15 minutes, the remainder being unsedated.

Safety

Midazolam: There were no adverse reactions.

Saline: One patient had a period of bigeminy about 2 to 3 minutes after injection lasting approximately 20 to 30 seconds.

Diazepam: Patient reported slight dizziness just after injection, felt to be probably drug related. Ventricular fibrillation occurred in patient during the angiogram, and he was easily defibrillated with no subsequent effects. This was considered remotely drug related, since it occurred later in time than the peak effect of the drug. Patient #015 had mildly increased mean arterial pressure during the procedure, considered remotely drug related.

Summary and Conclusions

This was a randomized, double-blind, parallel group evaluation of midazolam sedative and hemodynamic effects during cardiac catheterization. Measurement of changes from control values in hemodynamic parameters were compared between midazolam and saline. There were no statistically significant differences between midazolam and diazepam in any parameter.

The mean degree of sedation did not reach the moderate level in any group. Most patients in the midazolam group and half of the diazepam patients reached a mild level of sedation.

The only probably drug-related adverse reaction was dizziness reported by one diazepam patient. There was no venous irritation. Changes in vital signs were not significant.

This study demonstrated that midazolam was a safe and effective intravenous sedative to use in patients with stable coronary artery disease undergoing cardiac catheterization. Cardiac hemodynamics were minimally altered to a clinically insignificant degree.

Pooled Study Summary

Study nos. 103 and 111, Protocol 2243A

Title: A comparison of Midazolam and Diazepam for Intravenous Sedation During Angiography

Subjects

Thirty five patients undergoing coronary angiography were the subjects of this study. In the midazolam group there were 18 subjects consisting of 11 males and 7 females with a mean age of 52.4 years (range 28-62). In the diazepam group there were 17 subjects consisting of 11 males and 6 females with a mean age of 53.5 years (range 17-73).

Results

Differences Between the Centers

The patients in study 103 received relatively higher midazolam and lower diazepam doses than the patients in study 111. A relatively shorter procedure time also existed in study 103. Consequently, the patients in study 103 performed the one and two hour postangiography Trieger Tests about one-half hour earlier on the average than the patients in study 111. Therefore, the evaluation of recovery from sedation for the patients in study 103 could have been affected by a higher total dose of midazolam and an earlier assessment of the recovery after midazolam administration. This might explain the differing Trieger Test results at the two centers. In study 103 the midazolam-treated patients recovered slower than the diazepam group as measured by the Trieger Test; whereas, in study 111 the reverse relationship occurred.

Drug Dose and Time Required to Induce Sedation

The midazolam-treated patients required a significantly shorter time and less test medication than the diazepam group. Respective initial mean sedation doses were 0.121 mg/kg and 0.212 mg/kg and mean induction times were 3.5 minutes and 8.36 minutes.

Physician's Assessment

The quality of sedation, patient cooperation, muscle relaxation and patient tolerance were rated as "good" to "excellent" for both groups. There were no significant differences between groups.

Patient's Assessment

More midazolam patients had impaired recall of the procedure than in the diazepam group. The majority of midazolam-treated patients either had no

recall or partial recall of the procedure at one and 24 hours following angiography at one hour and 24 hours after the procedure, a greater number of patients in the midazolam group rated the quality of sedation as "excellent" than the diazepam group. The majority of patients in both groups preferred to have the procedure performed the same way again, if necessary.

Trieger Test

Differences between centers have been elaborated upon. When the results were pooled, the patterns of recovery were similar for both groups.

Safety

All changes in vital signs from baseline were transient and clinically insignificant. Patient of study 111 (midazolam) developed confusion, disorientation, amnesia and anxiety in the middle of his procedure. This lasted for one hour and he recovered spontaneously. Patient of study 111 (midazolam) had transient apnea, followed by confusion and disorientation for 1/2 hour which resolved spontaneously. Three diazepam-treated patients developed mild phlebitis or vein irritation at the IV site. There was no vein irritation or phlebitis in the diazepam group.

Summary and Conclusions

In this multicenter study midazolam was used to provide sedation during coronary angiography. Midazolam-treated patients required a mean initial sedation dose of 0.121 mg/kg and a mean induction time of 3.5 minutes compared with a mean initial sedation dose of 0.212 mg/kg and a mean time of 8.36 minutes required by the diazepam group to reach the sedative end point. The physician's assessment indicated no significant differences between the two drugs; however, the patient's assessment revealed that a greater number of patients in the midazolam group experienced diminished recall of the procedure and rated the quality of sedation as "excellent."

The pooled results indicated similar patterns of psychomotor recovery from sedation in the two groups although an apparent prolongation of recovery in the midazolam group in one study could have been related to a higher total dose of midazolam coupled with an earlier assessment time related to a shorter procedure time. Recovery from the sedative effects may be dose-dependent.

All changes in vital signs were transient and clinically insignificant. Two midazolam-treated patients developed confusion and one of these experienced brief apnea; however, both recovered spontaneously. Three diazepam-treated patients developed mild phlebitis or vein irritation at the IV site.

The results of this study showed that IV midazolam is as effective as diazepam as a sedative in coronary angiography. It may have an earlier onset of action than IV diazepam and had no venous irritation. It was safely employed and demonstrated some possibly dose-related delay in recovery from its sedative effects.

Study No. 103

Title: A Comparison of Midazolam and Diazepam for Intravenous Sedation During Angiography

Investigator: Philip A. Ludbrook, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in patients undergoing coronary angiography for the first time.

Subjects

There were 10 non-pregnant females and 12 males, ranging in age from 17 to 73 years (ASA I, II or III). In the midazolam-treated group there were 6 males and 6 females with a mean age of 52.3 years (range 28-62). In the diazepam group there were 6 males and 4 females with a mean age of 54.1 years (range 17-73).

Study Drugs:

Patients were randomly assigned to midazolam or diazepam treatment groups. Based on the patient's age and clinical condition, the investigator slowly titrated (2-3 minutes) the initial and incremental doses (1-10 mg) of either drug until the patient's speech became slurred or thickened but the patient was still responsive to verbal commands. An additional 1-5 mg of test medication was administered, if necessary, to maintain adequate sedation during angiography.

Experimental Design

This was a randomized, double-blind parallel group study. The drug dose and time required to induce sedation were calculated. Drug effects were assessed by the physician and the patient. Immediately following angiography, the physician assessed (a) patient's cooperation, (b) muscle relaxation, (c) quality of sedation and (d) patient's overall tolerance of the procedure. One hour after angiography and one day later patients evaluated (a) quality of sedation, (b) pain during the procedure, (c) memory of the procedure, and (d) whether they would elect to undergo a future angiography, if necessary, the same way. Recovery from sedation was assessed by the Trieger Test which was completed by the patient before medication (baseline) and at 60 and 120 minutes following the completion of angiography. Each Trieger Test was evaluated for the number of dots missed and the total deviation (mm) from the dots.

Continuous electrocardiographic monitoring was carried out in the angiography laboratory. Vital signs were monitored before, during and after angiography. Significant changes from baseline in vital signs were identified as possible adverse experiences (mild: 7, 20% but 30% change; moderate: 30% but 50% change; and severe; 50% change from baseline). The intravenous injection site was examined 7-14 days following the procedure for possible venous irritation.

Results

Deviations from Protocol

Protocol deviations were observed in four patients. Two patients had a history of previous angiographic procedure (patients - midazolam) and were excluded from efficacy analyses. A 17 year old patient (diazepam) met all protocol requirements except for age and was included in all analyses. A fourth patient (midazolam) had surgery 5 to 6 hours after angiography and could not complete the 24 hour post-angiography evaluation. Available data were included in all analysis possible for this patient.

Drug Dose and Time Required to Induce Sedation

Comparable initial levels of sedation were reached by mean doses of 0.144 mg/kg of midazolam and 0.183 mg/kg of diazepam. The sedative end point was attained in a mean time of 4.4 minutes with midazolam and 6.8 minutes with diazepam. Midazolam-treated patients required an additional mean dose of 0.037 mg/kg to maintain adequate sedation compared with 0.056 mg/kg for the diazepam group. The mean total sedation dose was 0.18 mg/kg for the midazolam group and 0.239 mg/kg for the diazepam group.

Physician's Assessment

The quality of sedation, muscle relaxation, patient's cooperation, and overall tolerance were rated as "good" to "excellent" in both treatment groups.

Patient's Assessment

At one hour and 24 hours following angiography, the majority of midazolam-treated patients had no recall or only partial recall of the procedure. A greater number of midazolam patients experienced diminished recall of the procedure than in the diazepam group. The quality of sedation was rated "excellent" by both groups. All patients in both groups preferred to have the procedure performed the same way again and both test groups reported little or no pain associated with the angiography.

Trieger Test

At two hours following angiography midazolam patients missed significantly more dots than the diazepam group. At two hours the diazepam group was recovered according to the two parameters in this test, whereas, the midazolam group still had elevated values compared to baseline.

Safety

The only adverse experiences were changes in vital signs. Most changes in vital signs were transient and clinically insignificant. None of the patients required any corrective measures. None of the patients had any clinically significant respiratory depression or hypotension. There were no clinically significant changes between treatments. No patient had clinical evidence of vein irritation or phlebitis at the intravenous injection site.

Summary and Conclusions

This randomized, double-blind study compared the use of intravenous midazolam with IV diazepam to provide sedation during coronary angiography. Midazolam provided "good" to "excellent" sedation and was equally effective as diazepam. Midazolam patients required 0.144 mg/kg to reach the sedative end point compared with 0.183 mg/kg required by the diazepam group. Comparable levels of sedation were achieved in 4.4 minutes with midazolam and 6.8 minutes with diazepam. At one hour and 24 hours following the procedure, a greater number of midazolam patients had impairment of recall of the procedure than diazepam patients. Recovery from sedation, as measured by the Trieger Test, was slower in the midazolam group. There were no clinically significant adverse experiences in either group in this study. The results of this study showed that IV midazolam was safely used to provide sedation and was as effective as diazepam.

Study No. 111

Title: A Comparison of Midazolam and Diazepam for Intravenous Sedation During Angiography

Investigator: Thomas J. Ryan, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in patients undergoing coronary angiography for the first time.

Subjects

There were 13 patients (ASA I, II, and III) in the study which was still in progress at the time of submission. There were 5 males and 1 female in the midazolam group with a mean age of 52.7 years (range 45-61). In the diazepam group there were 5 males and 2 females with a mean age of 52.7 years (range 44-62).

Study Drugs: See Study 103.

Experimental Design: See Study 103.

ResultsDeviations from Protocol

Patient (diazepam) was found to have significant left main trunk coronary artery disease and underwent emergency surgery. The investigator could not complete the proper subsequent follow-up of the patient; however, available data was analyzed.

Drug Dose and Time Required to Induce Sedation

Comparable initial levels of sedation were reached by mean doses of 0.098 mg/kg of midazolam and 0.242 mg/kg of diazepam. One patient in the midazolam-treated group and three diazepam-treated patients required an additional 0.009 mg/kg and 0.025 mg/kg of drug, respectively, during angiography to maintain adequate sedation. The sedative end point was attained in 2.63 minutes with midazolam and 9.93 minutes with diazepam. The midazolam-treated patients required a significantly shorter time and smaller amount of test drug to attain the sedative end point than the diazepam group.

Physician's Assessment

The quality of sedation, patient's cooperation, muscle relaxation and patient's tolerance were rated as "good" to "excellent" for both groups. There were no significant differences between groups.

Patient's Assesment

One hour following angiography, all six midazolam patients rated the quality of sedation as "excellent" compared with only 3 out of 7 diazepam-treated patients. One hour following angiography, a greater number of patients in the midazolam group had impaired recall of the procedure (5 of 6) than diazepam patients (1 of 7). By 24 hours, the diazepam group added one patient with impaired recall. Little or no pain was experienced by all patients reporting in both groups. All midazolam patients would elect to undergo a future procedure the same way while 2 of 6 repondents answered negatively at 24 hours in the diazepam group.

Trieger Test

Midazolam-treated patients missed fewer dots and had less deviation at one and two hours following angiography than on the baseline test. Diazepam-treated patients missed more dots and had more deviation than on the baseline test.

Safety

Table 1

Clinical Adverse Experiences

	Number of Patients	
	<u>Midazolam</u>	<u>Diazepam</u>
<u>Relationship to Test Drug - Possible or Probable</u>		
<u>Miscellaneous</u>		
Amnesia	1	0
Confusion	2	0
Anxiety	1	0
<u>Integumentary</u>		
Phlebitis at injection site	0	1
Pain during injection	0	1
<u>Respiratory</u>		
Itching Nose	0	1
Apnea	1	0
Respiration Rate Increase	5	4
Respiration Rate Decrease	5	5
<u>Cardiovascular</u>		
Pulse Increase	2	2
Pulse Decrease	0	1
MAP Decrease	3	7
Phlebitis	0	1
Hematoma at IV site	0	1
Tenderness of Vein	0	2
Redness of vein	0	1
Induration of Vein	0	1
<u>Relationship to Test Drug - Remote</u>		
<u>Gastrointestinal</u>		
Vomiting	1	0

Patient (midazolam .144 mg/kg) became confused and disoriented in the middle of the procedure. He also developed amnesia for the events of the preceding weeks and acute anxiety. The episode lasted for approximately one hour; however, the procedure was completed and he recovered spontaneously.

(midazolam .068 mg/kg had transient apnea approximately 4 minutes after the administration of the test drug. She did not require corrective

treatment. Subsequently, she became confused and disoriented for approximately 1/2 hour. She recovered spontaneously with no sequelae. Three diazepam patients (4, 7, 13) developed mild phlebitis or vein irritation at the IV site. Respiratory rate, pulse rate and mean arterial pressure fluctuated more than 20% from baseline intermittently; however, these changes were transient and clinically insignificant. None of the patients in either group had any clinically significant cardiovascular problems, except for the phlebitis described above.

Summary and Conclusions

This randomized, double-blind study compared the use of intravenous midazolam with IV diazepam to provide sedation during coronary angiography. This study was still in progress at the time of submission. Thirteen patients were included in this report. The midazolam-treated patients required a significantly shorter time and less amount of test drug to induce sedation than the diazepam group. The sedative end point was achieved with 0.098 mg/kg of midazolam in 2.63 minutes for the average patient compared with 0.242 mg/kg of diazepam in 9.93 minutes. The physician's assessment showed no significant difference between the two test medications. A greater number of midazolam patients rated the quality of sedation as "excellent" and experienced impaired recall of the procedure than the diazepam group. Recovery from sedation, as measured by the Trieger Test, was slower in the diazepam group. Patient ... (midazolam) experienced a transient episode of confusion, anxiety and retrograde amnesia; however, recovery was spontaneous and did not hamper the procedure. Patient ... (midazolam) experienced transient apnea followed by a brief period of confusion; however, recovery was spontaneous and the procedure was completed. Three diazepam-treated patients developed mild phlebitis or vein irritation at the IV site. Vital signs changes were transient and clinically insignificant.

The study showed that IV midazolam was a somewhat better sedative than diazepam, producing more impairment of recall of the procedure. There was less irritation at the IV site than in the diazepam group.

Overall Evaluation and Conclusions

Effectiveness

The clinical investigation of midazolam, when administered intravenously as an adjunct to local anesthetic agents, evaluated the safety and effectiveness of the drug for inducing sedation (slurred speech) in patients undergoing diagnostic endoscopic or cardiovascular procedures. The endoscopic procedures included bronchoscopy, gastroscopy and cystoscopy. The cardiovascular procedures included cardiac catheterization and angiography. Some of the parameters evaluated included sedation, patient cooperation, degree of pain associated with the procedure, amnesia and recovery from sedation. The dose required to reach the sedative end point of slurred speech and time to induction were also recorded.

The sedative properties of midazolam were evaluated in 30 clinical studies involving 749 patients who received midazolam (330 patients), diazepam (336 patients), placebo (73 patients), or normal saline (10 patients). In all studies, diazepam served as the reference drug. In addition, two protocols (2237A and 2237B) also specified placebo reference groups.

TABLE I
NUMBER OF PATIENTS

INVESTIGATOR	STUDY #	TOTAL	MIDAZOLAM	DIAZEPAM	PLACEBO (MIDAZOLAM)	PLACEBO (DIAZEPAM)	OTHER
Protocol 22344 - Bronchoscopy without Meperidine Premedication							
*Steinberg, H.	106	40	20	20	--	--	--
Robertson, J.K.	108	16	8	8	--	--	--
Amad, M.	112	4	3	1	--	--	--
Kvale, P.A.	121	23	11	12	--	--	--
Protocol 2235A - Bronchoscopy with Meperidine Premedication							
*Khan, F.A.	107	22	12	10	--	--	--
*Salchun, O.J.	117	21	10	11	--	--	--
*Jenkinson, S.J.	118	21	10	11	--	--	--
*Marlencheck, W.I.	123	24	11	13	--	--	--
Protocol 2235A - Cystoscopy without Meperidine Premedication							
*Lawson, R.K.	105	43	22	21	--	--	--
Evans, A.T.	113	28	13	15	--	--	--
*Wain, A.J.	119	40	20	20	--	--	--
*Chasapis, G.	150	40	20	20	--	--	--
Protocol 2237A - Cystoscopy with Meperidine Premedication (Females)							
*Witherington, R.	116	40	10	10	10	10	--
*Witherington, R.	126	10	2	3	3	2	--
Protocol 2237B - Cystoscopy with Meperidine Premedication (Males)							
Fair, W.R.	124	21	5	5	6	5	--
*Corssen, G.	125	41	10	11	10	10	--
Hanno, P.M.	127	14	4	3	3	4	--
Lawson, R.K.	128	19	5	4	5	5	--
Protocol 2238A - Gastroscopy without Meperidine Premedication							
Lanzo, F.L.	101	27	14	13	--	--	--
*Dunn, D.G.	110	41	20	21	--	--	--
Isenberg, J.I.	120	41	20	21	--	--	--
Protocol 2239A - Gastroscopy with Meperidine Premedication							
*White, P.F.	102	21	11	10	--	--	--
*Morissey, J.F.	104	20	10	10	--	--	--
Protocol 2241A - Cardioversion without Meperidine Premedication							
Lee, T.	109	5	1	4	--	--	--
Protocol 2247A - Cardiac Catheterization with Meperidine Premedication							
*Gensini, G.	114	22	10	12	--	--	--
*Hendrix, G.	115	20	10	10	--	--	--
*Lusbrook, P.A.	122	20	10	10	--	--	--
Protocol 1032 - Cardiac Catheterization without Meperidine Premedication - Hemodynamic Study							
*Fragen, R.	007 ⁶	30	10	10	--	--	10(1)
Protocol 2243A - Angiography without Meperidine Premedication							
*Lusbrook, P.A.	103	22	12	10	--	--	--
Ryan, T.J.	111	13	6	7	--	--	--

(1) 0.9% Saline
* Pivotal Study

Procedurally, all studies, with the exception of 009-Fragen, were similar. The test drug was administered slowly over a 2-3 minutes period until the sedative end point of slurred speech was reached. The time required to reach the end point and the dose of test drug administered were recorded. The study design was randomized, double-blind, parallel control.

Following the procedure, the physicians, who did not know which test drug had been administered, assessed the sedative properties of the test drugs.

One hour and 24 hours after the procedure, the endoscopic patients assessed the sedative - amnestic properties of the test drugs. In addition, in a questionnaire answered on the following day, endoscopic patients were asked whether they could recall events before, during and after the procedure.

The cardiovascular procedure studies did not utilize this questionnaire, nor did they evaluate the amnestic properties of the drugs. Furthermore, in the angiography study of Doctor Fragen, the patients did not evaluate sedation. His study was a special one which examined the cardiovascular effects of intravenous midazolam.

Recovery from sedation was measured by the Trieger Test in all studies except Doctor Fragen's. This test was completed by patients before medication and at one and two hours following completion of the endoscopy.

All adverse experiences were recorded and in all studies but Doctor Fragen's a follow-up examination was conducted for venous irritation or phlebitis.

The efficacy evaluations included results from 7 multicenter endoscopic protocols and 2 multicenter cardiovascular protocols (see Table 1). All studies under a protocol were included in the pooled efficacy results except for Dr. Ahmad's study (#112) under Protocol 2234A and Dr. Isenberg's study (#120) under Protocol 2238A. Dr. Ahmad's study was terminated after the enrollment of only four patients. The randomization code and sequential assignment of the test drugs was compromised in Dr. Isenberg's study since the drug shipment was divided incorrectly between two study sites. Due to the limited number of patients studied (one midazolam and four diazepam) the results of the cardioversion study (Dr. Lee, Protocol 2241A) were not included in the efficacy analyses.

There were two principal protocols for each endoscopic procedure. Protocols 2235A, 2237A, 2237B and 2239A allowed premedication with meperidine while no premedication was allowed in Protocols 2234A, 2236A and 2238A. The study results show that the mean end point of sedation (slurred speech) was attained in from 2.8 to 4.8 minutes in the seven studies. The dose of midazolam was 27% less in premedicated patients; however, the induction time was 24% longer than in unpremedicated patients. There was a more narrow dose range when meperidine premedication was used.

The overall mean induction dose was 0.091 mg/kg in premedicated patients and the mean induction time was 4.1 minutes. In unpremedicated patients the mean induction dose was 0.116 mg/kg and the mean induction time was 3.3 minutes. In the endoscopy studies, for patients below age 40, the mean midazolam dose needed was 0.161 mg/kg compared with 0.118 mg/kg when meperidine was used as premedication. For patients over 59 years of age, the mean midazolam dose was 0.114 mg/kg compared with 0.084 mg/kg of midazolam when meperidine was used as premedication. There is a 26-27% lower requirement, therefore, in dose for patients over 59 compared with those less than 40 whether or not meperidine is used. Ten percent of midazolam patients (26 of 255) required an additional dose of the test drug to maintain sedation. Most patients requiring a maintenance dose were in bronchoscopy studies where some investigators had difficulty with the management of the patients since meperidine premedication was not allowed. In other instances, requirements for additional doses were due to the length of time required for completion of the procedure. Overall, in the cardiovascular studies, 35% of midazolam-treated patients (16 of 46) required additional doses to maintain sedation for completion of the procedure because of the extended length of angiographic and cardiac catheterization procedures.

The induction time was significantly shorter for midazolam-treated patients than for diazepam-treated patients. In the physicians' assessments of sedation about 80% or more of midazolam and diazepam-treated patients were evaluated as "good" or "excellent" for all parameters.

The midazolam-treated patients rated sedation as being significantly better than did those patients treated with diazepam on the one-hour questionnaire in two of seven multicenter studies (protocols 2234A and 2235A) and on the 24-hour questionnaire in two of seven multicenter studies (protocols 2235A and 2236A). Overall 90% of patients in both test and reference control groups answered affirmatively as to whether they were willing to undergo a future procedure the same way again. Overall, 208 of 256 (81.2%) midazolam-treated patients reported no pain compared with 160 of 261 (61.3%) diazepam-treated patients.

In the two multicenter cardiovascular studies (protocols 2242A and 2243A) midazolam treated patients rated quality of sedation as being significantly better than did diazepam-treated patients, one hour after the procedure. On the 24 hour assessment, quality of sedation was rated significantly better by midazolam-treated patients in only one of the two multicenter studies (protocol 2243A). There were no significant differences between treatment groups in the degree of pain associated with the procedure and in the number of patients who were willing to undergo a future procedure the same way again in the cardiovascular studies.

Midazolam-treated patients had no recall of the endoscope in 71.3% of cases (179 out of 251 midazolam-treated patients).

Safety

There were 29 studies in which 719 total patients received midazolam (320 patients), diazepam (326 patients) or placebo (73 patients). The safety evaluation of Dr. R. Fragen's study (009) will be reviewed at the end of this section. Tables 2A and 2B lists all clinical adverse experiences and their incidence, grouped by body system. The significant adverse experiences will be discussed.

TABLE 2A

CLINICAL ADVERSE EXPERIENCES

	<u>MIDAZOLAM</u>		<u>DIAZEPAM</u>		<u>PLACEBO (MIDAZOLAM)</u>		<u>PLACEBO (DIAZEPAM)</u>	
	<u>No.</u> <u>Pts.</u>	<u>Per-</u> <u>cent</u>	<u>No.</u> <u>Pts.</u>	<u>Per-</u> <u>cent</u>	<u>No.</u> <u>Pts.</u>	<u>Per-</u> <u>cent</u>	<u>No.</u> <u>Pts.</u>	<u>Per-</u> <u>cent</u>
<u>CARDIOVASCULAR</u>								
Hypotension	4	1.3	2	0.6	-	-	-	-
Pulse Increased	104	32.5	106	32.5	2	5.4	6	16.7
Pulse Decreased	46	14.4	40	12.3	8	21.6	3	8.3
Map Decreased	93	29.1	58	17.8	2	5.4	4	11.1
Map Increased	27	8.4	37	11.3	3	8.1	4	11.1
Asystole	-	-	1	0.3	-	-	-	-
Myocardial infarct	1	0.3	-	-	-	-	-	-
Bradycardia	1	0.3	-	-	-	-	-	-
Arrhythmia	-	-	1	0.3	-	-	-	-
<u>RESPIRATORY</u>								
Sore Throat	1	0.3	-	-	-	-	-	-
Coughing	1	0.3	-	-	-	-	-	-
Itching Nose	-	-	1	0.3	-	-	-	-
Laryngospasm	-	-	1	0.3	-	-	-	-
Laryngitis	1	0.3	-	-	-	-	-	-
Epiglottitis	1	0.3	-	-	-	-	-	-
Bronchospasm	1	0.3	-	-	-	-	-	-
Respiratory Depression	1	0.3	-	-	-	-	-	-
Apnea	5	1.6	5	1.5	-	-	-	-
Shallow Respirations	1	0.3	-	-	-	-	-	-
Airway Obstruction	1	0.3	-	-	-	-	-	-
Respiration Rate Increase	104	32.5	112	34.4	9	24.3	8	22.2
Respiration Rate Decrease	82	25.6	76	23.3	5	13.5	5	13.9
<u>LOCAL IV SITE</u>								
Phlebitis at injection site	-	-	2	0.6	-	-	-	-
Inflammation at injection site	-	-	1	0.3	-	-	-	-
Pain during injection of drug	1	0.3	5	1.5	-	-	-	-
Hematoma at IV site	-	-	1	0.3	-	-	-	-
Tenderness of vein	7	2.2	14	4.3	2	5.4	-	-
Redness of vein	7	2.2	5	1.5	-	-	-	-
Induration of vein	8	2.5	8	2.5	-	-	-	-

TABLE 2B
CLINICAL ADVERSE EXPERIENCES

	<u>MIDAZOLAM</u>		<u>DIAZEPAM</u>		<u>PLACEBO</u> <u>(MIDAZOLAM)</u>		<u>PLACEBO</u> <u>(DIAZEPAM)</u>	
	<u>No.</u> <u>Pts.</u>	<u>Per-</u> <u>cent</u>	<u>No.</u> <u>Pts.</u>	<u>Per-</u> <u>cent</u>	<u>No.</u> <u>Pts.</u>	<u>Per-</u> <u>cent</u>	<u>No.</u> <u>Pts.</u>	<u>Per-</u> <u>cent</u>
<u>CNS AND RELATED</u>								
Excessive Sedation	3	0.9	1	0.3	-	-	-	-
Deep Sedation	2	0.6	-	-	-	-	-	-
Unresponsive	1	0.3	-	-	-	-	-	-
Drowsy	3	0.9	1	0.3	-	-	-	-
Lethargy	1	0.3	-	-	-	-	-	-
Weak	1	0.3	1	0.3	-	-	-	-
Confusion	2	0.6	-	-	-	-	-	-
Amnesia (Retrograde)	1	0.3	-	-	-	-	-	-
Anxiety	1	0.3	-	-	-	-	-	-
Agitated	-	-	1	0.3	-	-	-	-
Argumentative	1	0.3	-	-	-	-	-	-
Headache	4	1.3	3	1.0	-	-	-	-
Clenching of Jaws	1	0.3	-	-	-	-	-	-
Dizziness	1	0.3	1	0.3	1	2.7	1	2.8
<u>GASTROINTESTINAL</u>								
Dry mouth	1	0.3	-	-	1	2.7	-	-
Taste acid	1	0.3	-	-	-	-	-	-
Throat pain	-	-	1	0.3	-	-	-	-
Nausea	4	1.3	3	1.0	-	-	-	-
Vomiting	3	0.9	3	0.9	-	-	-	-
<u>MISCELLANEOUS</u>								
Nosebleeds	1	0.3	-	-	-	-	-	-
Apathy	-	-	1	0.3	-	-	-	-
Chest pain	1	0.3	1	0.3	-	-	-	-
Rash legs	-	-	1	0.3	-	-	-	-
Swollen arm/it	-	-	1	0.3	-	-	-	-
Phlebitis (Other than local IV site)	-	-	2	0.6	-	-	-	-
Blood loss	1	0.3	-	-	-	-	-	-
Blurred vision	1	0.3	-	-	-	-	-	-
Conjunctivitis	-	-	1	0.3	-	-	-	-
Tinnitus	-	-	1	0.3	-	-	-	-
<u>NUMBER OF PATIENTS TREATED</u>	320	-	326	-	37	-	36	-

Clinically Significant Hypotension

Four midazolam and two diazepam-treated patients developed clinically significant hypotension. The majority of these patients also received meperidine in addition to the test drug. Where both agents were used it was felt that the combined effects of both meperidine and the benzodiazepine may have contributed to the development of these reactions.

Table 3Clinically Significant Hypotension

<u>Study #</u>	<u>Age (yrs)</u>	<u>Test Drug</u>	<u>Adjuvant Therapy</u>	<u>Comments</u>
102/6	66	Midazolam 0.100 mg/kg	Meperidine 1.0 mg/kg Local Anesthetic	- Investigator treated this with Narcan®.
107/4	60	Midazolam 0.091 mg/kg	Meperidine 0.909 mg/kg Local Anesthetic	- Investigator treated this with dopamine.
112/2	54	Midazolam 0.181 mg/kg	Local Anesthetic	- Spontaneous recovery No treatment required.
117/13	72	Midazolam 0.095 mg/kg	Meperidine 1.3 mg/kg Local Anesthetic	- The patient also had apnea which investigator treated with Narcan®.
129/9	61	Diazepam 0.142 mg/kg	Local Anesthetic	- Spontaneous recovery No treatment required.
137/11	67	Diazepam 0.066 mg/kg	Meperidine 0.676 mg/kg Local Anesthetic	- Spontaneous recovery No treatment required.

TABLE 28

CLINICAL ADVERSE EXPERIENCES

	MIDAZOLAM		DIAZEPAM		PLACEBO (MIDAZOLAM)		PLACEBO (DIAZEPAM)	
	No. Pts.	Per- cent	No. Pts.	Per- cent	No. Pts.	Per- cent	No. Pts.	Per- cent
<u>CNS AND RELATED</u>								
Excessive Sedation	3	0.9	1	0.3	-	-	-	-
Deep Sedation	2	0.6	-	-	-	-	-	-
Unresponsive	1	0.3	-	-	-	-	-	-
Drowsy	3	0.9	1	0.3	-	-	-	-
Lethargy	1	0.3	-	-	-	-	-	-
Weak	1	0.3	1	0.3	-	-	-	-
Confusion	2	0.6	-	-	-	-	-	-
Amnesia (Retrograde)	1	0.3	-	-	-	-	-	-
Anxiety	1	0.3	-	-	-	-	-	-
Agitated	-	-	1	0.3	-	-	-	-
Argumentative	1	0.3	-	-	-	-	-	-
Headache	4	1.3	5	1.5	-	-	-	-
Clenching of Jaws	1	0.3	-	-	-	-	-	-
Dizziness	1	0.3	1	0.3	1	2.7	1	2.8
<u>GASTROINTESTINAL</u>								
Dry mouth	1	0.3	-	-	1	2.7	-	-
Taste acid	1	0.3	-	-	-	-	-	-
Throat pain	-	-	1	0.3	-	-	-	-
Nausea	4	1.3	5	1.5	-	-	-	-
Vomiting	3	0.9	3	0.9	-	-	-	-
<u>MISCELLANEOUS</u>								
Hiccoughs	1	0.3	-	-	-	-	-	-
Apathy	-	-	1	0.3	-	-	-	-
Chest pain	1	0.3	1	0.3	-	-	-	-
Rash legs	-	-	1	0.3	-	-	-	-
Swollen armpit	-	-	1	0.3	-	-	-	-
Phlebitis (Other than local IV site)	-	-	2	0.6	-	-	-	-
Blood loss	1	0.3	-	-	-	-	-	-
Blurred vision	1	0.3	-	-	-	-	-	-
Conjunctivitis	-	-	1	0.3	-	-	-	-
Tinnitus	-	-	1	0.3	-	-	-	-
<u>NUMBER OF PATIENTS TREATED</u>	320	-	326	-	37	-	36	-

Clinically Significant Respiratory Depression and/or Apnea

Five midazolam and five diazepam-treated patients developed apnea. Two midazolam-treated patients required corrective measures and had their bronchoscopies cancelled. All other patients recovered spontaneously. Both midazolam-treated patients received meperidine. Two additional midazolam-treated patients (study 112, patient and study 113, patient) had minor transient respiratory difficulty; however, they underwent their endoscopic procedures and had no significant sequelae.

TABLE 4

<u>Study and Pt. ECP #</u>	<u>Age (yrs.)</u>	<u>Test Drug</u>	<u>Adjuvant Therapy</u>	<u>Comments</u>
107/12	50	Midazolam 0.083 mg/kg	Meperidine 0.833 mg/kg and Local Anesthetic	- Patient was treated with Narcan® and breathing resumed spontaneously.
109/1	30	Midazolam 0.136 mg/kg	—	- Spontaneous recovery. No treatment required.
111/9	61	Midazolam 0.068 mg/kg	Local Anesthetic	- Spontaneous recovery. No treatment required.
117/13	72	Midazolam 0.095 mg/kg	Meperidine 1.3 mg/kg IM and Local Anesthetic	- Patient was treated with Narcan®
130/19	79	Midazolam 0.161 mg/kg	* Local Anesthetic	- Spontaneous recovery. No treatment required.
109/2	57	Diazepam 0.101 mg/kg	—	- Spontaneous recovery. No treatment required.
117/1	56	Diazepam 0.072 mg/kg	Meperidine 0.575 mg/kg and Local Anesthetic	- Spontaneous recovery. No treatment required.
130/9	76	Diazepam 0.259 mg/kg	Local Anesthetic	- Spontaneous recovery. No treatment required.
130/14	66	Diazepam 0.219 mg/kg	Local Anesthetic	- Spontaneous recovery. No treatment required.
130/18	69	Diazepam 0.286 mg/kg	Local Anesthetic	- Spontaneous recovery. No treatment required.

Central Nervous System and Related Side Effects

Three elderly midazolam-treated patients experienced excessive sedation and two others experienced deep sedation. Another became unresponsive to painful stimuli and required treatment with Narcan. All of the above patients, except one, received meperidine as premedication and the investigators felt that the combined drug sedative effects produced excessive sedation.

TABLE 5

CNS and Related Side Effects

<u>Adverse Experience</u>	<u>Study and Pt. ECP #</u>	<u>Age (yrs)</u>	<u>Test Drug</u>	<u>Adjuvant Therapy</u>	<u>Comments</u>
Deep Sedation and Hypotension	107/4	60	Midazolam 0.091 mg/kg	Meperidine 0.909 mg/kg	-Pt. also developed hypotension which was reversed by dopamine.
Deep Sedation and Apnea	107/12	50	Midazolam 0.083 mg/kg	Meperidine 0.833 mg/kg	-Pt. also had transient apnea and he received Narcan® and breathing resumed spontaneously.
Excessive Sedation	105/16	69	Midazolam 0.134 mg/kg	--	-One hour after the procedure patient could be aroused only with painful stimuli. No specific treatment required.
Excessive Sedation	125/29	96	Midazolam 0.083 mg/kg	Meperidine 0.833 mg/kg	-Alzheimer's disease.
Excessive Sedation	128/7	82	Midazolam 0.057 mg/kg	Meperidine 1.14 mg/kg	-No specific treatment required.
Excessive Sedation	128/5	78	Diazepam 0.016 mg/kg	Meperidine 0.77 mg/kg	-Excessive sedation following meperidine injection therefore test drug dose was reduced.
Unresponsiveness	124/12	65	Midazolam 0.152 mg/kg	Meperidine 0.759 mg/kg	Narcan® was given to reverse the effects.

Three midazolam-treated patients (study #107, patient , study #101, patient study 110, patient and one diazepam-treated patient (study 101, patient) experienced drowsiness following the study, but none of them required any specific corrective measures. Patient of study 111 (midazolam) experienced a transient period of confusion, anxiety and retrograde amnesia for about one hour, with spontaneous recovery. Assuming the correct dose of meperidine to be about 1 mg/kg, then all of the premedicated patients in table 5 got correct doses except for patients of study 128, who was slightly over. The mean dose of midazolam overall was 0.161 mg/kg for patients over 59 which was reduced to 0.113 mg/kg when premedicated with meperidine. There were four midazolam-treated patients who were premedicated and were over 59. Of these two got a dose greater than the mean and two got less than the mean dose, for premedicated patients. Additionally, the one premedicated 50 year old patient clearly got a lower dose of midazolam than would be anticipated for the age. Therefore lowering of the dose of midazolam may not provide complete freedom from excessive sedation in patients who have had concomitant narcotics.

Patient of study 117 (midazolam) experienced clenching of the jaws twice during the administration of a local anesthetic to the pharynx and once immediately following the injection of midazolam. This lasted only 1-2 minutes and the patient underwent the subsequent procedure uneventfully. According to the investigator, this was not related to the test drug, since the clenching of the jaws was observed prior to the injection of midazolam.

Other CNS and related side effects were minor, transient and did not require any specific corrective measures.

Local Side Effects at the Intravenous Site

Table 6 suggests that midazolam produces less pain during injection and less irritation at the intravenous site.

Gastrointestinal Side Effects

As seen in Table 2B, minor transient side effects such as nausea and vomiting were seen with almost equal frequency in both midazolam and diazepam-treated patients.

Other Side Effects

Patient of Study 123 (midazolam) had mild hiccoughs, which subsided spontaneously after 15-30 seconds. Another midazolam-treated patient (study 121,) experienced pharyngeal bleeding and bronchospasm which forced the cancellation of the bronchoscopy. According to the investigator, this had no relation to the test drug administration and resulted from a pre-existing condition.

Patient of study 107 was found to have epiglottitis and laryngitis during the examination immediately prior to the bronchoscopy; therefore, the investigator cancelled the procedure.

Changes in Vital Signs

The changes in vital signs of 20% from baseline are included in Table 2A under the headings of respiratory and cardiovascular adverse experiences. Changes in respiratory rate, pulse rate and mean arterial pressure were the most common adverse experiences. The majority of these changes were transient and clinically insignificant. Tables 7A, 7B and 7C summarize these changes by the phase of the study and severity of these changes. Most changes did not require any specific treatment and had no significant clinical implication. During induction, changes were for the most part, comparable between the two test drug groups. Clinically significant hypotension and apnea has already been commented on.

TABLE 6

Local Side Effects at the Intravenous Site

	<u>Midazolam</u>		<u>Diazepam</u>	
	<u>No.</u>	<u>Per-</u>	<u>No.</u>	<u>Per-</u>
	<u>Pts.</u>	<u>cent</u>	<u>Pts.</u>	<u>cent</u>
Number of Patients treated	320		326	-
Phlebitis at site of injection	-	-	2	0.6
Inflammation of injection site	-	-	1	0.3
Pain during injection of study drug	1	0.3	5	1.5
Hematoma at IV site	-	-	1	0.3
Tenderness of vein	7	2.2	14	4.3
Redness of vein	7	2.2	9	2.8
Induration of vein	8	2.5	8	2.5

TABLE 7A

CHANGES IN RESPIRATORY RATE

	<u>MIDAZOLAM</u>		<u>DIAZEPAM</u>		<u>PLACEBO (MIDAZOLAM)</u>		<u>PLACEBO (DIAZEPAM)</u>	
	<u>No.</u>	<u>Per- Pts. cent</u>	<u>No.</u>	<u>Per- Pts. cent</u>	<u>No.</u>	<u>Per- Pts. cent</u>	<u>No.</u>	<u>Per- Pts. cent</u>
<u>NUMBER OF PATIENTS TREATED</u>	320	-	326	-	37	-	36	-
<u>DURING INDUCTION</u>								
Increase (20-30%)	4	1.3	7	2.1	1	2.7	-	-
Increase (30-50%)	-	-	5	1.5	-	-	-	-
Increase (>50%)	-	-	1	0.3	-	-	-	-
Decrease (20-30%)	14	4.4	13	4.0	-	-	-	-
Decrease (30-50%)	1	0.3	3	0.9	-	-	-	-
Decrease (>50%)	1	0.3	-	-	-	-	-	-
<u>DURING MAINTENANCE</u>								
Increase (20-30%)	39	12.2	51	15.6	4	10.8	4	11.1
Increase (30-50%)	20	6.3	23	7.1	1	2.7	-	-
Increase (>50%)	17	5.3	13	4.0	-	-	-	-
Decrease (20-30%)	40	12.5	41	12.6	2	5.4	3	8.3
Decrease (30-50%)	11	3.4	11	3.4	-	-	-	-
Decrease (>50%)	6	1.9	3	0.9	-	-	-	-
<u>DURING RECOVERY</u>								
Increase (20-30%)	24	7.5	31	9.5	3	8.1	3	13.9
Increase (30-50%)	14	4.4	17	5.2	2	5.4	1	2.8
Increase (>50%)	18	5.6	16	4.9	-	-	-	-
Decrease (20-30%)	34	10.6	24	7.4	3	8.1	2	5.6
Decrease (30-50%)	12	3.8	16	4.9	2	5.4	-	-
Decrease (>50%)	1	0.3	12	3.7	-	-	-	-

Ranges include lower limit and upper limit

TABLE 7B

CHANGES IN PULSE RATE

	<u>MIDAZOLAM</u>		<u>DIAZEPAM</u>		<u>PLACEBO (MIDAZOLAM)</u>		<u>PLACEBO (DIAZEPAM)</u>	
	<u>No.</u>	<u>Per- Pts., cent.</u>	<u>No.</u>	<u>Per- Pts., cent.</u>	<u>No.</u>	<u>Per- Pts., cent.</u>	<u>No.</u>	<u>Per- Pts., cent.</u>
<u>NUMBER OF PATIENTS TREATED</u>	320	-	326	-	37	-	36	-
<u>DURING INDUCTION</u>								
Increase (20-30%)	7	2.2	9	2.8	-	-	-	-
Increase (30-50%)	2	0.6	4	1.2	-	-	-	-
Increase (>50%)	-	-	1	0.3	-	-	-	-
Decrease (20-30%)	2	0.6	2	0.6	-	-	-	-
Decrease (30-50%)	1	0.3	-	-	-	-	-	-
Decrease (>50%)	-	-	-	-	-	-	-	-
<u>DURING MAINTENANCE</u>								
Increase (20-30%)	35	10.9	33	10.1	1	2.7	3	8.3
Increase (30-50%)	33	10.3	38	11.7	-	-	1	2.8
Increase (>50%)	22	6.9	19	5.8	-	-	-	-
Decrease (20-30%)	12	3.8	9	2.8	1	2.7	2	5.6
Decrease (30-50%)	5	1.6	4	1.2	-	-	-	-
Decrease (>50%)	1	0.3	-	-	-	-	-	-
<u>DURING RECOVERY</u>								
Increase (20-30%)	24	7.5	28	8.6	1	2.7	2	5.6
Increase (30-50%)	18	5.6	22	6.7	-	-	1	2.8
Increase (>50%)	13	4.1	7	2.1	-	-	-	-
Decrease (20-30%)	29	9.1	27	8.3	8	21.6	2	5.6
Decrease (30-50%)	7	2.2	5	1.5	-	-	-	-
Decrease (>50%)	-	-	1	0.3	-	-	-	-

Ranges include >lower limit and <upper limit

Fragen Study (009)

In the Fragen study there were no significant differences in hemodynamic parameters, between the two test drug groups and dynamics were only minimally altered.

TABLE 7CCHANGES IN MEAN ARTERIAL PRESSURE

	<u>MIDAZOLAM</u>		<u>DIAZEPAM</u>		<u>PLACEBO (MIDAZOLAM)</u>		<u>PLACEBO (DIAZEPAM)</u>	
	<u>No.</u>	<u>Per-</u>	<u>No.</u>	<u>Per-</u>	<u>No.</u>	<u>Per-</u>	<u>No.</u>	<u>Per-</u>
	<u>Pts.</u>	<u>cent</u>	<u>Pts.</u>	<u>cent</u>	<u>Pts.</u>	<u>cent</u>	<u>Pts.</u>	<u>cent</u>
<u>NUMBER OF PATIENTS TREATED</u>	320	-	326	-	37	-	36	-
<u>DURING INDUCTION</u>								
Increase (20-30%)	2	0.6	1	0.3	-	-	-	-
Increase (30-50%)	1	0.3	-	-	-	-	-	-
Increase (>50%)	-	-	-	-	-	-	-	-
Decrease (20-30%)	7	2.2	3	0.9	1	2.7	-	-
Decrease (30-50%)	1	0.3	2	0.6	-	-	-	-
Decrease (>50%)	-	-	-	-	-	-	-	-
<u>DURING MAINTENANCE</u>								
Increase (20-30%)	11	3.4	20	6.1	2	5.4	2	5.6
Increase (30-50%)	8	2.5	11	3.4	1	2.7	-	-
Increase (>50%)	2	0.6	-	-	-	-	2	5.6
Decrease (20-30%)	34	10.6	22	6.7	-	-	-	-
Decrease (30-50%)	15	4.7	6	1.8	-	-	1	2.8
Decrease (>50%)	-	-	-	-	-	-	-	-
<u>DURING RECOVERY</u>								
Increase (20-30%)	6	1.9	9	2.8	-	-	1	2.8
Increase (30-50%)	2	0.6	2	0.6	-	-	-	-
Increase (>50%)	1	0.3	1	0.3	-	-	1	2.8
Decrease (20-30%)	51	15.9	36	11.0	1	2.7	3	8.3
Decrease (30-50%)	17	5.3	7	2.1	-	-	-	-
Decrease (>50%)	-	-	-	-	-	-	-	-

Ranges include lower limit and upper limit

Package Insert

Only sections applicable to the studies of sedation for endoscopies and short procedures will be commented on here.

Description

Not applicable.

Clinical Pharmacology

The statement: "When used intravenously as a sedative for endoscopic or other short therapeutic or diagnostic procedures, the end point of slurred speech can be attained within 2.8 to 4.8 minutes, depending on the total dose administered and whether or not preceded by narcotic premedication." is correct but requires elaboration to prevent a misleading inference. The induction time range is inclusive of all the mean times in all the pooled endoscopic or short procedural studies with the exception of Fragen's cardiovascular hemodynamic study and Lee's aborted cardioversion study, including premedication with meperidine and procedures not using meperidine premedication. While the mean induction time was dependent on the total dose administered and whether or not preceded by narcotic premedication, the relationships of induction time to these two factors are opposite. In general, when meperidine was used as a premedicant, the dose of midazolam required for sedation was less than the dose of midazolam required by patients who did not receive premedication. It also followed that while the dose was less in the premedicated patients, generally (with the exception of cystoscopy), the induction time was longer than in unpremedicated patients (See Table I). The mean age and weights in corresponding types of pooled studies with and without meperidine premedication are comparable; therefore, the only variables which relate to mean induction time are dose of midazolam and use of meperidine.

Package Insert

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TABLE I

Mean Induction Time Related to Mean Dose
of Midazolam in Pooled Studies

<u>Protocol No.</u>	<u>Pooled Study</u>	<u>Premedica- tion With Meperidine</u>	<u>Mean Age (range)</u>	<u>Mean Wt. (kg) (range)</u>	<u>Mean Dose (mg/kg)</u>	<u>Mean Ind. Time (min.)</u>
2236A	Cystoscopy	No	52.2 (17-86)	71.4 (45-157)	.152	3.9
2243A	Angiography	No	52.4 (28-62)	85.7 (58-115)	.121	3.5
2238A	Gastroscopy	No	49.1 (19-73)	72.8 (46-115)	.164	2.8
2234A	Bronchoscopy	No	54.8 (21-85)	71.5 (50-113)	.110	3.0
2337A	Cystoscopy	Yes	52.4 (28-88)	70.7 (53-94)	.090	2.9
2237B	Cystoscopy	Yes	60.0 (18-96)	72.3 (44-114)	.104	4.2
2242A	Cardiac Catheterization	Yes	53.8 (31-68)	75.2 (52-103)	.072	4.83
2239A	Gastroscopy	Yes	50.5 (20-76)	69.2 (44-132)	.095	4.3
2235A	Bronchoscopy	Yes	49.8 (25-72)	69.8 (41-123)	.094	4.4

This relationship of induction time to premedication is not apparent from the phrase "... depending on the total dose administered and whether or not preceded by narcotic premedication"; and it would be appropriate to augment this phrase with an additional statement clarifying the fact that premedicated patients required lower induction doses but had longer induction times than unpremedicated patients.

Indications

In the last sentence of this section it states that "Seventy-three percent of the patients in the endoscopy studies had no recall of introduction of the scope." This should be 71% (179/251).

The indication "for conscious sedation prior to short surgical, diagnostic, therapeutic or endoscopic procedures, such as bronchoscopy, gastroscopy, cystoscopy, urinary angiography and cardiac catheterization, either alone or in conjunction with a narcotic" should be modified since the actual studies included only diagnostic, endoscopic or cardiovascular procedures. Therefore,

the words "short surgical" and "therapeutic" should be deleted. We do not know how patients would respond under the pain and stress of conscious surgical and therapeutic interventions.

Contraindications: Not Applicable.

Warnings: Adequate.

Precautions: Adequate.

Adverse Reactions

To the list of reactions, hypotension should be added, especially when premedicated with narcotic. This occurred in four cases, three of which were premedicated with meperidine (study 102, study 107, study 117, and one of which was not premedicated with meperidine (study 112,

Dosage and Administration

The paragraph entitled "INTRAVENOUSLY Endoscopic or Cardiovascular Procedures" requires some elaboration. In the right hand column it states "Generally 0.1 to 0.15 mg/kg is adequate, but up to 0.2 mg/kg may be given, particularly when concomitant narcotics are omitted." An additional statement should be added to the effect that when a dose of 0.15 mg/kg is exceeded there is an increased frequency of depressed respiration and drowsiness. (See Table 2).

TABLE 2

Dose Related Adverse Reactions
When Concomitant Meperidine Was Not Given

<u>Induction dose (mg/kg)</u>	<u>Study #</u>	<u>Patient #</u>	<u>Reaction</u>
<u>Induction dose 0.15 mg/kg</u>			
0.217	101		lethargic, weak, dizzy
0.203	101		drowsiness following study
0.206	101		drowsiness following study
0.181	112		respiratory depression and hypotension
0.169	113		shallow respirations
0.161	150		apnea following induction
<u>Induction dose 0.15 mg/kg</u>			
0.134	105		excessive sedation after procedure
0.144	111		confusion
0.068	111		apnea

How Supplied: Not Applicable.

Conclusions

Effectiveness

1. The nine pooled studies are adequate and well-controlled as are the pivotal individual studies listed by the sponsor (see Table 1 in previous efficacy evaluation).
2. When used intravenously as a sedative for endoscopic or diagnostic procedures midazolam was as effective as was diazepam and the end point of sedation was more rapid following administration of midazolam than diazepam at comparable doses.
3. The end point of slurred speech was attained in the pooled endoscopic and diagnostic studies within mean times of 2.8 to 4.8 minutes.
4. The induction time depends on the total dose of midazolam.
5. The induction time also depends on whether induction is preceded by narcotic premedication, and in general the induction doses were smaller, but the induction times were longer when narcotic premedication was used.
6. In general, the desired end point of slurred speech was attained with a dose of less than 0.150 mg/kg of midazolam without narcotic premedication and the dose was proportionately less when meperidine premedication was used.
7. Midazolam was as effective as diazepam in producing a relaxed and cooperative patient as assessed by the physician.
8. Patients tended to rate the quality of sedation as better with midazolam and experienced less pain during the procedure than those patients who received diazepam.
9. Seventy one percent of the patients in the endoscopy studies had no recall of introduction of the scope, indicating effectiveness in inducing failure of recall of the procedure.

Safety

1. The majority of adverse experiences, as defined by the sponsor were changes in vital signs greater than 20% from baseline. Most of these were transient and of no clinical significance.
2. Midazolam, in the doses used, was as safe as diazepam in providing sedation during endoscopic and cardiovascular procedures, both with and without meperidine premedication.

3. In doses above 0.15 mg/kg there was an increased frequency of depressed respiration and drowsiness.
4. Clinically significant adverse experiences which occurred were:
 - a. Hypotension (especially with meperidine premedication)
 - b. Apnea
 - c. Respiratory depression
 - d. Shallow respiration
 - e. Excessive sedation
 - f. -Deep sedation
 - g. Unresponsiveness
 - h. Tenderness of vein - IV site
 - i. Redness of vein - IV site
 - j. Induration of vein - IV site

Recommendations

The use of midazolam for endoscopic and short diagnostic procedures is medically approvable. The draft package insert should be corrected as follows in a written communication to the sponsor:

1. Clinical Pharmacology

In the third paragraph of this section in the second sentence delete "other short therapeutic" since no intravenous sedative studies were conducted in therapeutic procedures, only diagnostic ones.

2. Clinical Pharmacology

The relationship of induction time to narcotic premedication is not apparent in the second sentence of the third paragraph in the phrase "depending on the total dose administered and whether or not preceded by narcotic premedication." An additional sentence should be added which states: "Premedicated patients required lower induction doses but had longer induction times than unpremedicated patients."

3. Indications

The indication "intravenously as an agent for conscious sedation prior to short surgical, diagnostic, therapeutic or endoscopic procedures, ..." should have the words "surgical" and "therapeutic" deleted, since no studies of these types of procedures were conducted and we do not know how patients would respond under the pain and stress of conscious surgical and therapeutic interventions.

4. In the last sentence of this section it states that "seventy-three percent of the patients in the endoscopy studies had no recall of introduction of the scope." This figure should be changed to seventy-one percent, since it represents 179 out of 251 patients.

5. Adverse Reactions

To the list of adverse reactions following intravenous administration add "hypotension, particularly when premedicated with a narcotic."

6. Dosage and Administration

In the subsection entitled "INTRAVENOUSLY Endoscopic or Cardiovascular Procedures," in the right hand column it states "generally 0.1 to 0.15 mg/kg is adequate, but up to 0.2 mg/kg may be given, particularly when concomitant narcotics are omitted." An additional statement should be added which states: "When a dose of 0.15 mg/kg is exceeded there is an increased frequency of depressed respiration and drowsiness."

Harvey Dickstein
Harvey Dickstein, M.D.

NDA 18-654

MFN-160

MFN-120

MFN-340

R/D HLDickstein 4/18/84

R/D Init. by PGWalters 4/18/84

FT OLA, JB, TD, KR W 1513N, 2478P, 1553N, 1559N, 1561N, 1564N, 1568N, 1570N,

1571N, 1574N, Archives 0084N and 0088N

Doc. Room 160

N 18654 -1

NDA

18-654

Approval

Letter +

FPL

18-654

DEC 20 1985

Hoffmann-LaRoche
Attention: Karen Church
Nutley, New Jersey 07110

Dear Ms. Church:

Reference is made to your new drug application dated December 15, 1985 submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Versed (midazolam hydrochloride) Injection.

We also acknowledge receipt of your additional communications dated September 4 and November 18, 1985, and additional submissions of the following:

- DRAFT package insert dated November 27, 1985,
- FINAL immediate container labels dated December 6, 1985, NDA 18-654
- DRAFT promotional copy dated December 16, 1985

We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on December 13, 1985. Accordingly, the application is approved, effective on the date of this letter.

The labeling should use "injection" in the title in place of "injectable". Also, the Description section should include the chemical name and graphic formula of the hydrochloride. These changes may be made at the next printing.

Please submit one market package of the drug when available.

You may not legally market the drug until final rulemaking procedures for scheduling under the Controlled Substances Act are enacted by the Drug Enforcement Administration.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 314.81 for an approved NDA.

Sincerely yours,

Paula Botstein MD

Paula H. Botstein, M.D.
Acting Deputy Director (Medical Affairs)
Office of Drug Research and Review
Center for Drugs and Biologics

VERSED®

brand of
midazolam HCl/Roche

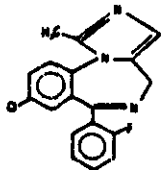
INJECTABLE

ROCHE

IV

DESCRIPTION: VERSED (brand of midazolam hydrochloride/Roche) is a water-soluble benzodiazepine available in a sterile parenteral dosage form for intravenous or intramuscular injection. Each ml contains midazolam hydrochloride equivalent to 5 mg midazolam compounded with 0.8% sodium chloride and 0.01% disodium edetate, with 1% benzyl alcohol as preservative; the pH is adjusted to approximately 3 with hydrochloric acid and, if necessary, sodium hydroxide.

Chemically, midazolam is 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine. It is a white to light yellow crystalline compound, insoluble in water; the hydrochloride salt is soluble in aqueous solutions. Midazolam has a calculated molecular weight of 325.78 and the following structural formula:



CLINICAL PHARMACOLOGY: VERSED is a short-acting benzodiazepine central nervous system depressant.

The effects of VERSED on the CNS are dependent on the dose administered, the route of administration, and the presence or absence of other premedications. Onset time of sedative effects after IM administration was 15 minutes, with peak sedation occurring 30 to 60 minutes following injection. In one study, when tested the following day, 73% of the patients who received VERSED intramuscularly had no recall of memory cards shown 30 minutes following drug administration; 40% had no recall of the memory cards shown 60 minutes following drug administration.

Sedation after IV injection was achieved within 3 to 5 minutes; the time of onset is affected by total dose administered and the concurrent administration of narcotic premedication. Seventy-one percent of the patients in the endoscopy studies had no recall of introduction of the endoscope; 62% of the patients had no recall of withdrawal of the endoscope.

When VERSED is given intravenously as an anesthetic induction agent, induction of anesthesia occurs in approximately 1.5 minutes when narcotic premedication has been administered and in 2 to 2.5 minutes without narcotic premedication or with sedative premedication. Some impairment in a test of memory was noted in 90% of the patients studied.

VERSED, used as directed, does not delay awakening from general anesthesia. Gross tests of recovery after awakening (orientation, ability to stand and walk, suitability for discharge from the recovery room, return to baseline trigger competency) usually indicate recovery within 2 hours but recovery may take up to 6 hours in some cases. When compared with patients who received thiopental, patients who received midazolam generally recovered at a slightly slower rate. Reaction time under stress (operating automobiles or other hazardous machinery) has not been studied. (See WARNINGS.)

The intravenous administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered.

In patients without intracranial lesions, induction with VERSED is associated with a moderate decrease in cerebrospinal fluid pressure (lumbar puncture measurements), similar to that seen following use of thiopental. Preliminary data in intracranial surgical patients with normal intracranial pressure but decreased compliance (subarachnoid screw measurements) show comparable elevations of intracranial pressure with VERSED and with thiopental during induction.

Measurements of intracranial pressure in patients without eye disease show a moderate lowering following induction with VERSED; patients with glaucoma have not been studied.

Usual intramuscular premedication doses of VERSED do not depress the ventilatory response to carbon dioxide stimulation to a clinically significant extent. Induction doses of VERSED depress the ventilatory response to carbon dioxide stimulation for 15 minutes or more beyond the duration of ventilatory depression following administration of thiopental. Impairment of ventilatory response to carbon dioxide is more marked in patients with chronic obstructive pulmonary disease (COPD). Sedation by intravenous VERSED does not adversely affect the mechanics of respiration (resistance, static recoil, mean lung volume measurements); total lung capacity and peak expiratory flow decrease significantly but static compliance and maximum expiratory flow at 50% of awake total lung capacity (V₅₀) increase.

In cardiac hemodynamic studies, induction with VERSED was associated with a slight to moderate increase in mean arterial pressure, cardiac output, stroke volume and systemic vascular resistance. Slow heart rates (less than 60/minute), particularly in patients taking propranolol for angina, tended to rise slightly; faster heart rates (e.g., 85/minute) tended to slow slightly.

The following preliminary pharmacokinetic data for midazolam have been reported. In normal subjects and healthy patients intravenous midazolam exhibited an elimination half-life of 1.2 to 12.3 hours, a large volume of distribution (0.95 to 6.8 L/kg) and a plasma clearance of 0.15 to 0.77 L/min/kg.

Following intravenous administration, less than 0.03% of the dose is excreted in the urine as intact midazolam. Midazolam is rapidly metabolized to 1-hydroxymethyl midazolam, which is excreted, with subsequent excretion in the urine. Approximately 45% to 57% of the dose is excreted in the urine as the conjugate of 1-hydroxymethyl midazolam, the major metabolite of midazolam. The half-life of elimination of 1-hydroxymethyl midazolam is similar to the parent compound. The concentration of midazolam is 10- to 30-fold greater than that of 1-hydroxymethyl midazolam after single IV administration.

Chemical effects of VERSED do not directly correlate with the blood concentrations of midazolam.

In a small group of patients (n = 11) with congestive heart failure, there appeared to be a 2- to 3-fold increase in the elimination half-life and volume of distribution of midazolam; however, the total body clearance of midazolam appeared to remain unchanged at a single 5-mg intravenous dose. There was no apparent change in the pharmacokinetic profile following the intravenous administration of 5 mg of midazolam to a small group of patients (n = 12) with hepatic dysfunction. There was a 1.5- to 2-fold increase in elimination half-life, total body clearance and volume of distribution in a small group of patients (n = 15) with chronic renal failure.

In a small group (n = 12) of surgical patients, aged 49 to 60 years old, given 0.2 mg/kg midazolam intravenously, there appeared to be a small increase in the volume of distribution and elimination half-life with little change in total body clearance compared to an equal number of younger surgical patients (aged 18 to 30).

The mean absolute bioavailability of midazolam following intramuscular administration is greater than 90%. The mean time of maximum midazolam plasma concentrations following intramuscular dosing occurs within 45 minutes postadministration. Peak concentrations of midazolam as well as 1-hydroxymethyl midazolam after intramuscular administration are about one-half of those achieved after equivalent intravenous doses. The pharmacokinetic profile of elimination after intramuscularly administered midazolam is comparable to that observed

following intravenous administration of the drug. Dose-linearity relationships have not been adequately defined.

Midazolam is approximately 97% plasma protein-bound in normal subjects and patients with renal failure. In animals, midazolam has been shown to cross the blood-brain barrier. In animals and in humans, midazolam has been shown to cross the placenta and enter into fetal circulation. It is not known whether midazolam is secreted in human milk.

INDICATIONS: Injectable VERSED is indicated—

- intramuscularly for preoperative sedation (induction of sleepiness or drowsiness and relief of apprehension) and to impair memory of peri-operative events;
- intravenously as an agent for conscious sedation prior to short diagnostic or endoscopic procedures, such as bronchoscopy, gastroscopy, cystoscopy, coronary angiography and cardiac catheterization, either alone or with a narcotic;
- intravenously for induction of general anesthesia, before administration of other anesthetic agents. With the use of narcotic premedication, induction of anesthesia can be attained with a relatively narrow dose range and in a short period of time. Intravenous VERSED can also be used as a component of intravenous supplementation of nitrous oxide and oxygen (balanced anesthesia) for short surgical procedures; longer procedures have not been studied.

When used intravenously, VERSED is associated with a high incidence of partial or complete upturn of recall for the next several hours. (See CLINICAL PHARMACOLOGY.)

CONTRAINDICATIONS: Injectable VERSED is contraindicated in patients with a known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma. Benzodiazepines may be used in patients with open angle glaucoma only if they are receiving appropriate therapy. (See CLINICAL PHARMACOLOGY.)

WARNINGS: PRIOR TO THE INTRAVENOUS ADMINISTRATION OF VERSED IN ANY DOSE, THE IMMEDIATE AVAILABILITY OF OXYGEN AND RESUSCITATIVE EQUIPMENT FOR THE MAINTENANCE OF A PATENT AIRWAY AND SUPPORT OF VENTILATION SHOULD BE ENSURED. Because intravenous VERSED depresses respiration (see CLINICAL PHARMACOLOGY) and because opioid agonists and other sedatives can add to this depression, VERSED should be administered as an induction agent only by a person trained in general anesthesia and should be used in conscious sedation only when a person skilled in maintaining a patent airway and supporting ventilation is present.

Injectable VERSED should not be administered to patients in shock or coma, or in acute alcohol intoxication with depression of vital signs.

The hazards of intra-arterial injection of VERSED solutions in humans are unknown; therefore, extreme precautions against unintentional intra-arterial injection should be taken. Extravasation should also be avoided.

Higher risk surgical patients or debilitated patients require lower dosages for induction of anesthesia, whether premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure have a 1.5- to 2-fold increase in elimination half-life, total body clearance and volume of distribution of midazolam. Patients with congestive heart failure have a 2- to 3-fold increase in the elimination half-life and volume of distribution of midazolam. Patients over the age of 65 years require lower dosages for induction of anesthesia, whether premedicated or not. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduced initial dosage of VERSED is recommended and the possibility of profound and/or prolonged effect should be considered. Concurrent use of barbiturates, alcohol or other central nervous system depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with a narcotic.

The decision as to when patients who have received injectable VERSED, particularly on an outpatient basis, may again engage in activities requiring complete mental alertness, operable hazardous machinery or drive a motor vehicle, must be individualized. Gross tests of recovery from the effects of VERSED (see CLINICAL PHARMACOLOGY) cannot be relied upon alone to predict reaction time under stress. This drug is never used alone during anesthesia and the contribution of other pre-operative drugs and events can vary. It is recommended that no patient operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia and surgery, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepine drugs (diazepam and chlorazepate) has been suggested in several studies. If this drug is used during pregnancy, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS: General: Because an increase in cough reflex and laryngospasm may occur with general endoscopic procedures, the use of a topical anesthetic agent and the availability of necessary countermeasures are recommended. The use of narcotic premedication is recommended for bronchoscopies.

Intravenous doses of VERSED should be decreased by 25% to 30% for elderly and debilitated patients. (See WARNINGS and DOSAGE AND ADMINISTRATION.) These patients will also probably take longer to recover completely after VERSED administration for the induction of anesthesia.

VERSED does not protect against the increase in intracranial pressure or circulatory effects noted following administration of succinylcholine.

VERSED does not protect against the increase in intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: To assure safe and effective use of benzodiazepines, the following information and instructions should be communicated to the patient when appropriate:

1. Inform your physician about any alcohol consumption and medicine you are now taking, including drugs you buy without a prescription. Alcohol has an increased effect when combined with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol during benzodiazepine treatment.
2. Inform your physician if you are pregnant or are planning to become pregnant.
3. Inform your physician if you are nursing.

Drug interactions: The hypnotic effect of intravenous VERSED is accentuated by premedication, particularly narcotics (e.g., morphine, meperidine and levorphanol) and also secobarbital and levorphanol (levorphanol and droperidol). Consequently, the dosage of VERSED should be adjusted according to the type and amount of premedication administered. (See DOSAGE AND ADMINISTRATION.)

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of intramuscular VERSED for premedication.

The use of VERSED as an induction agent may result in a reduction of the induction anesthetic requirement during maintenance of anesthesia. (See CLINICAL PHARMACOLOGY.)

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VERSED® (brand of midazolam HCl/Roche)

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium and does not protect against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, *n*-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, tetracaine HCl and Cetacaine) have been observed.

Drug/ laboratory test interactions: Midazolam has not been shown to interfere with results obtained in clinical laboratory tests.

Concomitant use of Verapamil:

Cardiogenesis, mutagenesis, impairment of fertility:
Ca. terogenesis: Midazolam maleate was administered with diet in mice and rats for two years at dosages of 1, 9 and 90 mg/kg/day. In female mice in the highest dose group there was a marked increase in the incidence of hepatic tumors. In high dose male rats there was a small but statistically significant increase in benign thyroid follicular cell tumors. Dosages of 9 mg/kg/day of midazolam maleate (25 times a human dose of 0.35 mg/kg) do not increase the incidence of tumors. The pathogenesis of induction of these tumors is not known. These tumors were found after chronic administration, whereas human use will ordinarily be of single or several doses.

Mutagenesis: Midazolam did not have mutagenic activity in *Salmonella typhimurium* (5 bacterial strains), Chinese hamster lung cells (V79), human lymphocytes, or in the micronucleus test in mice.

Impairment of fertility: A reproduction study in male and female rats did not show any impairment of fertility at dosages up to ten times the human IV dose of 0.35 mg/kg.

Pregnancy, Teratogenic effects: Pregnancy Category D. See WARNINGS section.

Segment II (toxicology studies, performed with midazolam maleate injectable in rabbits and rats at 5 and 10 times the human dose of 0.35 mg/kg, did not show evidence of teratogenicity.)

Neurotoxic effects: Studies in rats showed no adverse effects on reproductive parameters during gestation and lactation. Dosages tested were approximately 10 times the human dose of 0.35 mg/kg.

Labor and delivery: In humans, measurable levels of midazolam were found in maternal venous serum, umbilical venous and arterial serum and amniotic fluid, indicating placental transfer of the drug. Following intramuscular administration of 0.05 mg/kg of midazolam, both the venous and the umbilical arterial serum concentrations were lower than maternal concentrations.

The use of injectable VERSED in obstetrics has not been evaluated in clinical studies. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Patient use: Safety and effectiveness of VERSED in children below the age of 16 have not been established.

ADVERSE REACTIONS: Fluctuations in vital signs were the most frequently seen findings following premedication administration of VERSED and included decreased tidal volume and respiratory rate (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate. These are common occurrences during anesthesia and surgery and are affected by the tightening or loosening of the mask, instrumentation, intubation and use of succinylcholine drugs.

In the conscious sedation studies, hypotension occurred more frequently after IV administration of VERSED in patients concurrently premedicated with meperidine. It should be noted that VERSED does not modify the cardiovascular effects of neuromuscular blocking agents or the tachycardia and blood pressure rises seen during endotracheal intubation under light general anesthesia. During the clinical investigations, three cases (0.3%) of transient fall in blood pressure greater than 50% were reported during the induction phase.

The following adverse reactions were reported after intramuscular administration:

headache (1.3%)	Local effects of IM injection site
	pain (3.7%)
	induration (0.5%)
	redness (0.5%)
	muscle stiffness (0.3%)

The following adverse reactions were reported subsequent to intravenous administration:

headache (3.9%)	Local effects of the IV site
nausea (2.6%)	tenderness (5.6%)
vomiting (2.6%)	pain during injection (5.0%)
chills (1.3%)	redness (2.6%)
"overdose" (1.6%)	induration (1.7%)
headache (1.5%)	phlebitis (0.4%)
drowsiness (1.2%)	

Other adverse experiences, observed mainly following IV injection and occurring at an incidence of less than 1.0%, are as follows:

Respiratory: Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respiration, stridor, obstruction, tachypnea.

Cardiovascular: Bradycardia, premature ventricular contractions, vasovagal episode, tachycardia, chest rhythm.

Gastrointestinal: Acid taste, excessive salivation, retching.

Central nervous system: Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, agitation, anxiety, prostration, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, involuntary movements, muscle tremor, involuntary movements, shivering movements, slurred speech, dysphasia, slurred speech, dysphonia, paresthesia.

Special Senses: Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, light-headedness.

Integumentary: Numbness, hive-like elevation at injection site, swelling or itching of burning, warmth or coldness at injection site, rash, pruritus.

Musculoskeletal: Tremor, lethargy, chills, weakness, lathargy, faint feeling, hemiparesis.

DRUG ABUSE AND DEPENDENCE: Midazolam is subject to Schedule IV control under the Controlled Substances Act of 1970.

Midazolam was actively self-administered in primate models used to assess the possible reinforcing effects of psychoactive drugs.

Midazolam produced physical dependence of a mild to moderate intensity in cynomolgus monkeys after 5 to 10 weeks of administration. Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

OVERDOSEAGE: There have been no reports of injectable VERSED overdose. The manifestations of VERSED overdose are expected to be similar to those observed with other benzodiazepines and include sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma and respiratory effects on vital signs. No evidence of specific organ toxicity from VERSED overdose would be expected.

Treatment of overdose: Treatment of injectable VERSED overdose is the same as that followed for overdose with other benzodiazepines. Respiration, pulse rate and blood pressure should be monitored and general supportive measures should be employed. Attention should be given to the maintenance of a patent airway and support of ventilation. An intravenous infusion should be started. Should hypotension develop, treatment may include intravenous fluid ther-

apy, repositioning, judicious use of vasopressors appropriate to the clinical situation, if indicated, and other appropriate countermeasures. There is no information as to whether peritoneal dialysis, forced diuresis or hemodialysis are of any value in the treatment of midazolam overdose.

DOSEAGE AND ADMINISTRATION: Dosage should be individualized. In general, lower doses are required in elderly or debilitated patients. The dosage of intravenous VERSED administered should be adjusted according to the type and amount of premedication used. When intravenous use is indicated, oxygen, resuscitative equipment and personnel resources for the maintenance of a patent airway should be immediately available. (See WARNINGS.)

Injectable VERSED may be mixed in the same syringe with the following frequently used premedications: morphine sulfate, meperidine, atropine sulfate or scopolamine. Injectable VERSED is compatible with 5% dextrose in water, 0.9% sodium chloride, and isotonic Ringer's solution.

For intramuscular use: VERSED should be injected deep in a large muscle mass. Intravenous VERSED for conscious sedation should be administered slowly; rapid injection may cause respiratory depression or apnea requiring assisted or controlled ventilation. For induction of general anesthesia, the initial dose should be administered over 20 to 30 seconds for optimum effect. Extreme care should be taken to avoid intra-arterial injection or extravasation (see WARNINGS).

INTRAMUSCULARLY

For preoperative sedation (induction of sleepiness or drowsiness and relief of apprehension) and to impair memory of peri-operative events.

USUAL ADULT DOSE

For premedication the recommended dose of VERSED is 0.07 to 0.08 mg/kg IM (approximately 5 mg IM for an average adult) approximately one hour before surgery. Onset is within 15 minutes, peaking at 30 to 60 minutes. It can be administered concomitantly with atropine sulfate or scopolamine hydrobromide and reduced doses of Narcotics.

INTRAVENOUSLY

Endoscopic or Cardiovascular Procedures:

For conscious sedation, VERSED can be used either alone or together with a narcotic immediately before the procedure, with supplemental doses of VERSED to maintain the desired level of sedation throughout the procedure. For general anesthesia, the use of an appropriate topical anesthetic is recommended. For bronchoscopic procedures, the use of narcotic premedication is recommended.

Three dosage to desired sedative end point, i.e., slowing of speech, with slow administration immediately prior to the procedure. Generally 0.1 to 0.15 mg/kg is adequate, but up to 0.3 mg/kg may be given, particularly when concomitant narcotics are given. Doses in excess of 0.15 mg/kg may result in increased risk of respiratory depression or obtundation in elderly or debilitated patients. Additional maintenance doses may be given in increments of 25% of the initial dose to maintain the desired level of sedation.

Narcotic premedication results in less variability in patient response. Dosage should be lowered by about 25% to 50% if narcotic premedication is used. Patients 60 years or older may require lower doses (by about 20%) than younger patients.

Induction of Anesthesia:

For induction of general anesthesia, before administration of other anesthetic agents.

Individual response to the drug is variable, particularly when a narcotic premedication is not used. The dosage should be titrated to the desired effect according to the patient's age and clinical status.

(Unpremedicated Patients)

In the absence of premedication, an average adult under the age of 55 years will usually require an initial dose of 0.3 to 0.35 mg/kg for induction, administered over 20 to 30 seconds and allowing 2 minutes for effect. If needed to complete induction, increments of approximately 25% of the patient's initial dose may be used; induction may instead be completed with variable large maintenance doses. In resistant cases, up to 0.6 mg/kg total dose may be used for induction, but such large doses may prolong recovery.

Unpremedicated patients over the age of 55 years usually require less VERSED for induction; an initial dose of 0.2 mg/kg is recommended. Unpremedicated patients with severe systemic disease or other debilitation usually require less VERSED for induction. An initial dose of 0.2 to 0.25 mg/kg will usually suffice; in some cases, as little as 0.15 mg/kg may suffice.

Premedicated Patients

When the patient has received sedative or narcotic premedication, particularly narcotic premedication, the range of recommended doses is 0.15 to 0.35 mg/kg.

In average adults below the age of 55 years, a dose of 0.25 mg/kg, administered over 20 to 30 seconds and allowing 2 minutes for effect, will usually suffice.

The initial dose of 0.2 mg/kg is recommended for good risk (ASA I & II) surgical patients over the age of 55 years.

In some patients with severe systemic disease or debilitation, as little as 0.15 mg/kg may suffice.

Narcotic premedication frequently used during clinical trials included fentanyl (1.5 to 2 µg/kg IV, administered five minutes before induction), meperidine (dosage individualized, up to 0.15 mg/kg IM), meperidine (dosage individualized, up to 1 mg/kg IM) and levorolol (0.02 mg/kg IM). Sedative premedications were hydroxyzine pamoate (100 mg orally) and sodium succinylcholine (200 mg orally). Except for intravenous fentanyl, administered five minutes before induction, all other premedications should be administered approximately one hour prior to the time anticipated for VERSED induction.

Injectable VERSED can also be used during maintenance of anesthesia, for short surgical procedures, as a component of balanced anesthesia. Effective narcotic premedication is especially recommended in such cases. Long surgical procedures have not been studied.

Incremental injections of approximately 25% of the induction dose should be given in response to signs of lightening of anesthesia and repeated as necessary.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED: All package configurations contain midazolam hydrochloride equivalent to 5 mg midazolam/ml.

- 1 ml ampuls (5 mg)—boxes of 10 (NDC 0004-1078-01);
- 2 ml ampuls (10 mg)—boxes of 10 (NDC 0004-1045-01);
- 1 ml vials (5 mg)—boxes of 10 (NDC 0004-1074-01);
- 2 ml vials (10 mg)—boxes of 10 (NDC 0004-1075-01);
- 5 ml vials (25 mg)—boxes of 1 (NDC 0004-1075-02) and 10 (NDC 0004-1075-01);
- 10 ml vials (50 mg)—boxes of 1 (NDC 0004-1046-02) and 10 (NDC 0004-1046-01);
- 1 ml To-E-Ject® disposable syring (5 mg)—boxes of 10 (NDC 0004-1047-01);
- 2 ml To-E-Ject® disposable syring (10 mg)—boxes of 10 (NDC 0004-1047-01);
- 1 ml To-E-Ject® disposable syring (5 mg)—boxes of 10 (NDC 0004-1047-70);
- 2 ml To-E-Ject® disposable syringe Cartridges (10 mg)—boxes of 10 (NDC 0004-1047-70).

Supp.

Letters

FEB 25 1988

NDA 18-654/S-012

Hoffmann-La Roche Inc.
Nutley, NJ 07110

Attention: Karen K. Church
Associate Director
Drug Regulatory Affairs

Gentlemen:

Please refer to your supplemental new drug application dated September 13, 1987, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for VERSED (midazolam HCl) Injection.

The supplemental application provides for a proposed "Dear Doctor" letter, a proposed revised package insert and proposed educational program (S-012).

We also acknowledge your additional communications dated October 23 and November 11, 1987 amending the supplemental application and November 23, 1987 providing final printed labeling.

We have completed our review of this supplemental application as amended and it is approved. Please be advised that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

Philip G. Walters, M.D.
Acting Director
Division of Surgical-Dental
Drug Products
Office of Drug Research and Review
Center for Drug Evaluation and Research

cc: NDA 18-654

HFN-180

HFN-83 w/labeling

HFN-231 w/labeling

HFN-160/Scally

Doc Rm 160

R/D JPHannan 3457Y 02/19/88

R/D Init by GBoyer 2/22/88 PGWalters 2/23/88

F/T MJO 2/24/88

APPROVAL

AUG 20 1987

NDA 18-654/S-011

Hoffmann-La Roche Inc.
Nutley, NJ 07110

Attention: Mary E. Reilly
Senior Manager
Drug Regulatory Affairs

Gentlemen:

Please refer to your supplemental new drug application dated February 23, 1987, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Versad^R (midazolam HCl) Injection.

The supplemental application provides for an alternate supplier of the needle shield used to protect disposable syringes (S-011).

We have completed our review of this supplemental application and it is approved. Please be advised that you must comply with the requirements set forth under 21 CFR 314.50 and 314.51 for an approved NDA.

Sincerely yours,

Philip G. Walters, M.D.
Acting Director
Division of Surgical-Dental
Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

cc: NDA 18-654

~~MPH-160~~

MPH-160/Rigglesman

Doc Rm 160

R/D JPHannan 2974k 08/12/87

R/D Init by 83oyer 8/13/87; 9Poochikian 8/13/87;

CPHoiberg/PGWalters 8/14/87

Ft/MPatterson 8/17/87

APPROVAL

NDA 18-654/S-009 and S-010

MAY 26 1987

Hoffmann-La Roche Inc.
Nutley, NJ 07110

Attention: Mary E. Reilly
Senior Manager
Drug Regulatory Affairs

Gentlemen:

Please refer to your supplemental new drug applications dated December 22, 1986, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Versed (midazolam HCl) Injection.

We also acknowledge receipt of your amendments dated January 20, March 19 (providing final printed labeling), April 14, and April 28, 1987.

The supplemental applications provide for a dilute concentration of 1 mg midazolam/ml (S-009) and appropriate final printed labeling (S-010).

We have completed our review of these supplemental applications as amended and they are approved. Please be advised that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

Philip G. Walters, M.D.
Acting Director
Division of Surgical-Dental
Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

NDA 18-654

MFN-160, HFN-83 w/labeling, HFN-231 w/labeling

HFN-160/Scally/Greenman

HFN-120/Zinsitz

Doc Rm 160

R/D JPHannan 0128z 05/18/87

RD init by VGreenman 5/20/87; RDJoyce/GBoyer 5/20/87; SKoch 5/20/87;

JCKenealy 5/21/87; PGWalters 5/21/87

Ft/MPatterson 5/22/87

APPROVAL

CHEMIST'S REVIEW

1. ORGANIZATION: HFN-120 10.1
2. NDA NUMBER: 18-654
3. AF NUMBER: 14-324
4. SUPPLEMENT NUMBERS/DATES: 009; 010.
(12/22/86)
5. AMENDMENTS/REPORTS/DATES:
6. REC'D. BY CHEMIST: 1/15/87

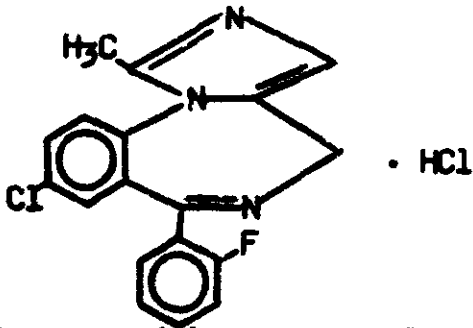
7. APPLICANT NAME AND ADDRESS:

Hoffmann-La Roche
Nutley, New Jersey 07110

8. NAME OF DRUG: Versed
9. NONPROPRIETARY NAME: midazolam hydrochloride

10. CHEMICAL NAME/STRUCTURE:

8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine hydrochloride



11. DOSAGE FORM(S): Injection
12. POTENCY(IES): 5 mg/mL as the hydrochloride
13. PHARM. CATEGORY: Hypnotic

14. HOW DISPENSED: (RX)

15. RECORDS AND REPORTS

CURRENT: X YES ___ NO
REVIEWED: ___ YES ___ NO

16. RELATED IND/NDA/DMF(S)

17. SUPPLEMENT(S) PROVIDES FOR:

manufacturing, packaging, control (S-010) and labeling (S-009) of a 1 mg/mL midazolam, as the hydrochloride, dosage strength in amber glass vials containing 2 mL, 5 mL or 10 mL.

18. COMMENTS:

The new dosage strength is a dilute solution of the approved 5 mg/mL Versed (midazolam hydrochloride) Injection. The specifications and tests methods used for the components of the new dilute solution and the methods used for the manufacturing and controls for the 1 mg/mL drug product are the same as previously used for the manufacture and control of the 5 mg/mL strength. However, the deficiencies cited in this review should be corrected before approval.

19. CONCLUSIONS AND RECOMMENDATIONS:

The application is approvable provided a satisfactory response is submitted for the deficiencies cited in this review which were conveyed by telephone (see Memorandum of Telephone Conversation dated 1/15/87).

20. REVIEWER:

NAME Francis A. Zinsitz SIGNATURE *Francis A. Zinsitz* DATE COMPLETED 1/16/87

Copies:

ORIG: NDA

HFN-120

HFN-120/F. A. Zinsitz / (1/16/87)

INIT: RCSchultz/

Pt/FAZ/(1/16/87)

DOC#31900

Consult file
Lear

1-16-87
02/9/87

JAN 22 1987

Pharm

Pharmacology and Toxicology Review

JUL 27 1984

NDA 18-654

Sponsor:

Hoffmann-La Roche, Inc.
Nutley, New Jersey 07110

Drug:

Midazolam Injectable (RO 21-3981)

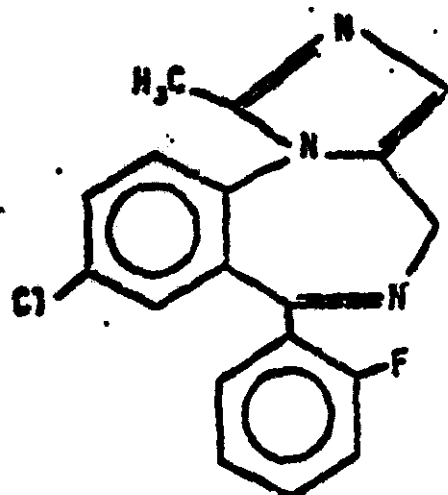
Category:

Anesthetic premedicant as a sedative and inductive agent

Administration:

Intramuscular or intravenous injection

Chemical Formula
and Name:



8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]-benzodiazepine

Chemical Forms Used in Preclinical Studies

RO 21-3981/000	Free base (Nutley formulation)
RO-21-3981/617	Free base (Basle formulation)
RO 21-3981/001	Maleate salt
RO 21-3981/002	Dihydrochloride salt
RO 21-3981/003	Monohydrochloride salt
RO 21-3981/602	Methanesulfonate salt

Related Drugs

The benzodiazepines. RO 21-3981 resembles triazolodiazepam derivatives; however, instead of a triazolo five member ring, it contains an imidazo five member ring. It also has a fluorine at the 2-phenyl position.

Related INDs:

Midazolam injectable:
Midazolam oral formulation:

Preclinical Pharmacological Studies with Midazolam

A. Neuropharmacology

Midazolam is an imidazobenzodiazepine whose salts are water soluble. When administered orally or parenterally to animals, it exhibits the characteristic pharmacological effects of marketed benzodiazepine drugs, i.e., anxiolytic (anti-conflict, calming effects), anticonvulsant, hypnotic, and muscle relaxant effects.

1. Continuous Avoidance Test in Rats

Midazolam maleate and diazepam have qualitatively and quantitatively similar effects in this test which measures a drug's ability to disinhibit behavior (avoidance) relative to conflict (electric shock). Typically, an anxiolytic drug at low dosage will increase the shock rate experienced by rats previously trained to avoid the shock rate experienced by rats previously trained to avoid the shock and then when the dose is raised to relatively high levels untoward effects such as sedation will result in greater escape failures. A wide separation of about 10 fold was observed for both drugs between the pharmacologically active dose and the neurotoxic dose.

2. Anticonvulsant, Pole Climbing and Rotorod Tests in Mice

Midazolam maleate (in water) and diazepam (in diazepam diluent) administered I.V. to mice were compared in the antimetrazol test for anticonvulsant activity and in the pole climbing and rotating rod tests for effects on muscle tone or coordination. Both drugs exhibited rapid onset of action in each test, with peak activity occurring at one minute after treatment. The potency of midazolam was 2-4 times that of diazepam at the peak time, but the duration of action for midazolam was shorter than that for diazepam. Specifically, in the antimetrazol test (which correlates well with clinical anxiolytic activity), diazepam was 2.5 times more potent than midazolam at one hour. In the pole climbing and rotarod tests diazepam was twice as potent as midazolam postdosing 30 and 15 minutes, respectively.

3. Muscle Relaxant Activity in Unanesthetized Cats

In unanesthetized cats the minimally effective dose of I.V. administered midazolam maleate was 0.25 mg/kg; diazepam was effective at 0.125 mg/kg. Both compounds showed a similar, rapid onset of activity (1-3 minutes). Duration of midazolam's activity was somewhat longer (46-90 minutes) than that of diazepam (20-35 minutes), a finding that was in contrast to results obtained in the mouse studies.

4. Hypnotic Activity in Mice

In mice diazepam and midazolam maleate I.V. displayed a rapid onset of hypnotic activity (0.3 minutes for diazepam and 1.1 minutes for midazolam, but the duration of action of midazolam (32 minutes) was only about half that of diazepam (57 minutes). The ED₅₀ (mg/kg I.V.) for diazepam was 18 mg/kg and for midazolam it was 70 mg/kg.

5. Neuromuscular and Spinal Cord Activity in Spinal or Decerebrate Cats

a) Neuromuscular Effects

In the unanesthetized spinal cat no effect on the amplitude of contraction of the muscle was produced by either midazolam maleate (0.01-30 mg/kg, I.V.) or diazepam (0.01-20 mg/kg, I.V.).

b) Dorsal Root Potential (DRP)

In the unanesthetized spinal or decerebrate cat, diazepam produced an increase in the amplitude and duration of the DRP, an effect that is interpreted as one indicator of an enhancement of presynaptic inhibition. The minimal effective dose was 0.05, I.V. and all doses up to 3 mg/kg were active. Midazolam maleate was qualitatively similar to diazepam but was less potent, with a minimal effective dose of 0.1 mg/kg, I.V. Both agents had an onset of action that occurred within 1 minute after injection; however, they differed markedly with respect to duration. After injection of midazolam, the DRP returned to control value within 30 minutes, whereas after injection of diazepam, the DRP continued to be enhanced for at least 4 hours.

c) Effect on the Gamma-Aminobutyric Acid (GABA) System

Current hypotheses propose that diazepam enhances presynaptic inhibition by means of an action on GABA neurons. In experiments related to this proposal, midazolam maleate was found to be qualitatively similar to diazepam. At the DRP peak-effect dose level of 1 mg/kg, I.V. in cats either agent reversed the depression of the DRP produced by the GABA blocking agent, bicuculline (0.3-0.6 mg/kg, I.V.). In addition, the enhancing action of either compound on the DRP was blocked by a GABA depletor, semicarbazide (200 mg/kg, I.V.) given 4 hours before the test drug.

B. Cardiovascular and Respiratory Studies in Dogs**1. Conscious Dogs**

Midazolam was administered by I.V. injection to female renal hypertensive dogs at doses of 0.3, 1, 3, and 10 mg/kg. All dogs appeared to be excited immediately after injection. The blood pressure was not altered. Heart rate, however, increased up to 20-25% after all dosages at varying times after injection. The heart rate was essentially normal 120 minutes post dosing.

2. Anesthetized Dogs

Midazolam maleate (4-20 mg/kg, i.v.) induced transient blood pressure (systolic and diastolic) reductions of 25-40 mm Hg in dogs anesthetized with barbiturate and 20-55 mm Hg in chloralosed dogs.

Decreases of approximately 30% in minute volume of respired air occurred in both groups of animals. Myocardial impairment was not reflected in the right atrial pressure of any of the treated animals. No significant effects on ECG were observed after midazolam administration.

Midazolam did not alter the pressor responses to injected epinephrine, norepinephrine, hypertensin or dimethylphenyl piperazinium (DMPP). Pressor responses to serotonin and to carotid artery occlusion were somewhat inhibited. Depressor responses to acetylcholine or histamine administration were essentially unaffected by midazolam.

C. Drug Interactions in Animals

Effects of midazolam alone or in combination with other drugs commonly used in preanesthetic medication.

1. Cardiovascular and Respiratory Studies

Animals:

Dogs: 4 females, weight 8.1-9.2 kg. The dogs were trained to be conscious when the experiments were carried out.

Dosage, route and duration of each drug:

- 1) Midazolam maleate - I.V. (0.15 mg/kg)
- 2) Hydroxyzine HCl (Vistaril, Pfizer) - I.M. (0.7 mg/kg)
- 3) Atropine sulfate (Burroughs Wellcome) - I.M. (0.007 mg/kg)
- 4) Meperidine HCl (Wyeth) - I.M. (1 mg/kg)

Sequence of Administration:

	No. of animals*	Time in Minutes		
		0	60	120
Protocol A	3	(2) (3) + (4)	saline	
Protocol B	4	(2) (3) + (4)	midazolam	
Protocol C	4	saline	saline	midazolam

*The animals were randomized and there were two days of rest between treatments.

Observed effects:

Systolic, diastolic and mean blood pressure were slightly decreased in protocol A 10 minutes after administration of drugs; whereas they were all elevated by 20-30 mm Hg in protocol B and C 10 minutes after dosing. The consistent, slight increase in blood pressure was transient. Fifteen minutes after midazolam treatment all returned to normal levels. Venous pressure decreased 15 minutes after midazolam in protocol B. Heart rate and pulse pressure remained relatively unchanged in all protocols. Respiratory rate was slightly elevated in protocol B and C 10 minutes after midazolam but by 30 minutes it returned to normal. Cardiac index (slightly decreased at 60 minutes in protocol B and C), stroke index (slightly decreased at 60 minutes in protocol B) and peripheral resistance index (slightly increased at 60 minutes in protocol A, B, and C) were found to be relatively competent. No observable changes were noted in the ECG wave form or blood gas data in the 3 protocols.

Conclusion:

The combination of midazolam and commonly used preanesthetic medications (atropine, meperidine, hydroxyzine) seems to exert only minor effects on cardiovascular and respiratory systems. There were transient increase in blood pressure and respiratory rate, but they returned to normal within a short period of time.

2. Dose Lethality Response of Midazolam, its Vehicle and Various Preanesthetics:**Animals:**

CD-1 mice from Charles River, Inc. weight 17-25 gm. 10 sex/dose level

Dosage:

Preanesthetics given orally:

- 1) Meperidine HCl: 200-630 mg/kg for males and females.
- 2) Atropine sulfate: 500-1000 mg/kg for males; 400-1250 mg/kg for female.

- 3) Meprobamate: 1000-2000 mg/kg for males and females.
- 4) Sodium Pentobarbital: 125-320 mg/kg for males and females.
- 5) Chlorpromazine HCl: 630-1250 mg/kg for males and females.

Midazolam maleate (3 mg/kg) or vehicle (0.024 ml/20 gm body weight) were administered I.V. 5 minutes following meperidine HCl, sodium pentobarbital or atropine sulfate, 30 minutes after chlorpromazine HCl and 60 minutes after meprobamate. All groups of animals were observed for 72 hours.

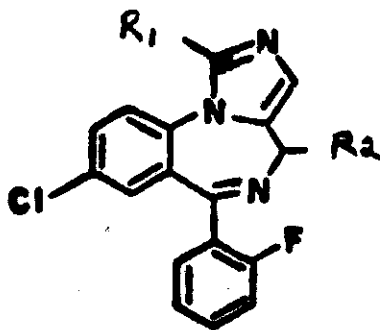
Conclusion:

An increase in lethality was consistently observed after combination of midazolam and chlorpromazine. Such an increase in lethality may also have occurred when midazolam was combined with atropine and pentobarbital. The cause of death was probably due to respiratory depression caused by high doses of the drugs.

Pharmacokinetics and Metabolism Studies with Midazolam

Studies have been conducted in vitro and in mouse, rat, and dog following intravenous administration of ¹⁴C midazolam.

In Vitro



	R ₁	R ₂
I.	CH ₃	H (midazolam)
II.	CH ₂ OH	H (Ro 21-6347)
III.	CH ₃	OH (Ro 21-5975)
IV.	CH ₂ OH	OH (Ro 22-0284)

Midazolam metabolites formed after in vitro incubation with rat liver 9000 X g supernatant.

In Vivo

1. Mouse (male, CD-1)

Labelled drug (4.6 mg/kg) was given intravenously in order to determine the tissue distribution of drug and metabolites during the first 60 minutes after its administration. Correlations were also sought between CNS activity and brain levels of drug and metabolites.

Midazolam accounted for 85% of the radioactivity in the brain at 1 minute. Within 10 minutes after I.V. dosing less than 50% of the radioactivity in plasma, brain, muscle, lung and fat was present as unchanged drug. At no time did the radioactivity in tissues exceed that in plasma. The half-life of intact drug in the brain was about 5 minutes. Moreover, the rate of disappearance of midazolam from the brain in the first 30 minutes was more rapid than its disappearance from the other tissues. Two metabolites RO 21-6347 and RO 21-5975 were also identified. The tissue levels, excluding brain, of RO 21-6347 were 5-10 fold higher than RO 21-5975. In general, very low concentrations of RO 21-5975 were found in brain with peak levels observed at 20 minutes post dosing. RO 21-6347 was present in brain at higher concentrations than midazolam or RO 21-5975 at 20 minutes.

With respect to the pharmacological CNS activity of midazolam and its two metabolites, it was found that the inhibition of anticonvulsant activity (metrazol and bicuculline) and ataxia were due to midazolam and not to RO 21-6347 or RO 21-5975.

2. Rat (male, CRCD)

Ether anesthetized rats were administered [¹⁴C]-midazolam (2.5 mg/kg) into the tail vein. Tissue samples were collected at 30 minutes, 1, 3, 5, 7 and 24 hours after dosing. Urine and feces were also collected.

Within 30 minutes about 50% of the radioactivity was found in the GI tract. At 24 hours, 8% was present in the GI tract while 80 and 9% were excreted in the feces and urine, respectively. Only about 2% of the administered dose remained in other tissues after 24 hours. Less than 1% of the dose was identified as midazolam, or unconjugated RO 21-6347 and RO 21-5975. The tissue distribution of radioactivity was highest in liver followed by kidney and fat. In another experiment using bile-duct cannulated rats, 50% of an I.V. dose of [¹⁴C]-midazolam was excreted in the bile during a 3 hour period following dosing. Phenolic metabolites were isolated from the bile and included RO 22-0284 and RO 21-5975. The biliary metabolites were excreted as glucuronide or sulfate conjugates.

3. Rat placental transfer of [¹⁴C] - midazolam

Fetal levels of radioactivity were less than levels in maternal blood or in the placenta suggesting a slower or limited penetration through the placenta.

4. Dog (male, Beagle)

Dogs were administered a single I.V. injection (10 mg/kg) of [¹⁴C] midazolam

Tri-exponential blood level time curves were obtained in dogs. A three compartment open system was described - one central and two peripheral. The

apparent half-life of elimination of midazolam was calculated to be 67 minutes. Fifty percent of the administered radioactivity was excreted in the feces. The total recovery of administered radioactivity ranged between 77-88% for 72 hours. RO 21-6347 was the major metabolite and accounted for 29-40% of the administered dose. Small amounts of midazolam and a trace of RO 21-5975 and RO 22-0284 were also present. In urine RO 21-6347 was excreted primarily as its glucuronide conjugate. It was not conjugated in the feces, but probably eliminated by the bile as its glucuronide and hydrolyzed by bacteria in the large intestine.

5. Human (men, 70-80 kg)

Five men were administered midazolam by I.V. injection of 0.13 mg/kg in 1 minute.

In 4 men, the blood fall off curves were triexponential and would be fitted to a three compartment system with elimination occurring from the central compartment. Midazolam is rapidly and extensively distributed and eliminated from the body with a half-life of 1.3 to 2.2 hours.

Three urinary metabolites were identified as glucuronides: RO 21-6347, RO 21-5975 and RO 22-0284. The major metabolite RO 21-6347, which accounted for 50% of the administered dose, was eliminated primarily within the first 12 hours. The overall recovery of the administered dose as this metabolite was 45-57% within 72 hours.

Conclusion:

Animal and clinical pharmacokinetic studies after I.V. injection of midazolam demonstrated that it and its metabolites appeared to be distributed rapidly and eliminated rapidly. Midazolam undergoes biotransformation by hydroxylation and conjugation before elimination from the body. The half-life in dogs was about 1 hour and in man it was about 1-2 hours. In dogs the urinary recovery of RO 21-6347 glucuronide was about 40% of the administered dose by 72 hours. In man, the urinary recovery of this metabolite was about 50% by 72 hours. Thus, the pharmacokinetic and metabolic profile of midazolam after I.V. injection appears similar for dog and man.

Preclinical Toxicology

1. Acute Parenteral Toxicity

Mice	I.V., I.M.
Rats	I.V., I.M.
Rabbits	I.V., I.M.
Dogs	I.V.

2. Single-Dose Studies

- Rabbits I.V. (venous irritation, 3 studies)
I.M. (muscle irritation, 2 studies)
- Dogs I.V. (venous irritation, 2 studies)

3. Pyramiding - Dose Toxicity

Dogs I.M.

4. Subchronic Toxicity

- Rats I.M. (2 weeks)
I.V. (5 weeks)
- Rabbits I.V. (2 weeks)
I.V. (2 week treatment; 2 week and 12 week observation)
I.V. (2 week treatment; 19 week observation)
- Dog I.M. (2 weeks)
I.V. (2 weeks)
I.V. or I.M. (5 weeks)

5. Reproduction Studies

- Rat oral Segment I (Fertility and Reproductive Performance)
- Rat I.V. Segment II (Teratology)
- Rabbit I.V. Segment II (Teratology)
- Rat I.V. Segment III (Perinatal and Postnatal Study)

6. Carcinogenicity Studies

- Mice oral (24 months interim report)
- Rat oral (24 months, interim report)

7. Mutagenicity Studies

- Bacteria *S. typhimurium* (Ames) (in vitro)

Chinese hamster (Y79) lung cells (in vitro)

Chromosome analysis human lymphocytes (in vitro)

Micronucleus test in mice (in vivo)

The following parenteral formulations were used in the various toxicity studies:

1. Formulation A (maleate salt)

<u>Ingredient</u>	<u>Concentration/ml</u>
Midazolam maleate	3.5 mg*
Tartaric acid	4.0 mg
Disodium edetate	0.1 mg
Sodium chloride	7.0 mg
Benzyl alcohol	0.01 ml
Sodium hydroxide (10%)	q.s. pH 3.3 + 0.1
Water	q.s. to 1 ml

*provides 2.5 mg base equivalents plus 3% excess

2. Formulation B (base, Nutley)

<u>Ingredient</u>	<u>Concentration/ml</u>
Midazolam (free base)	5.1 mg*
Disodium edetate	0.1 mg
Sodium chloride	8.0 mg
Benzyl alcohol	0.01 ml
HCl (v/v) q.s. pH 3.3 + 0.1	
Water q.s. to 1 ml	

*5.0 mg base plus 2% excess

3. Formulation C (base, Basle)

<u>Ingredient</u>	<u>Concentration/ml</u>
Midazolam (free base)	5.0 mg
Sodium chloride	5.0 mg
Benzyl alcohol	0.01 ml
HCl (25%)	4.088 mg
Sodium hydroxide (1 N)	q.s. pH 3.3 + 0.1
Water	q.s. to 1 ml

Acute Parenteral Toxicity

1. Species	Formulation	Route	Sex	LD50 (mg/kg of base equivalents)
<u>Mouse</u> (CD-1, CF-1)	A (maleate)	I.V. I.M.		34-70 ^a 25
	A (maleate)	I.V.	M F	44 (40-47) 41 (36-49)
	B (base, Nutley)	I.V.	M F	42 (36-49) 44 (42-46)
	C (base, Basle)	I.V.	M F	43 (39-48) 48 (43-53)
	RO 5606 (impurity of Ab)	I.V.	F	>1000
	A (maleate)	I.V.	M	86 (71-112) ^c
	RO 21-6164/001 (open ring)	I.V.	M	142 (130-154) ^c
<u>Rat</u> (F344)	A	I.V. I.M.		29 > 5
	B	I.V. I.M.		> 50 > 10
<u>Rabbit</u> (NZW)	A	I.V. I.M.		> 5d > 2.5
<u>Dog</u> (Beagle)	A	I.V.		>10 ^e

- a) Mortality usually occurred on the day of dosing. Signs included: decreased motor activity, hypnosis, and respiratory depression.
- b) RO 5606, an impurity of the maleate formulation, was found in concentrations of less than 0.1% after 2 years storage at room temperature of the maleate salt formulation.

Acute Parenteral Toxicity

1. Species	Formulation	Route	Sex	LD50 (mg/kg of base equivalents)
<u>Mouse</u> (CD-1, CF-1)	A (maleate)	I.V. I.M.		34-70 ^a 25
	A (maleate)	I.V.	M F	44 (40-47) 41 (36-49)
	B (base, Nutley)	I.V.	M F	42 (36-49) 44 (42-46)
	C (base, Basle)	I.V.	M F	43 (39-48) 48 (43-53)
	RO 5606 (impurity of Ab)	I.V.	F	> 1000
	A (maleate)	I.V.	M	86 (71-112) ^c
	RO 21-6164/CD1 (open ring)	I.V.	M	142 (130-154) ^c
<u>Rat</u> (CRCD)	A	I.V. I.M.		29 > 5
	B	I.V. I.M.		> 50 > 10
<u>Rabbit</u> (NZW)	A	I.V. I.M.		> 5d > 2.5
	A	I.V.		> 10 ^e
<u>Dog</u> (Beagle)	A	I.V.		> 10 ^e

- a) Mortality usually occurred on the day of dosing. Signs included: decreased motor activity, hypnosis, and respiratory depression.
- b) RO 5606, an impurity of the maleate formulation, was found in concentrations of less than 0.1% after 2 years storage at room temperature of the maleate salt formulation.

- c) At pH 6 or higher midazolam salts are entirely in the closed ring form while at lower pH the compound is in equilibrium between the closed and open ring forms. A reason for the decreased lethality of the open ring (RO 21-6164/001), although presumably in closed ring form at physiological pH, is that lethality was found to be volume dependent. More dilute solutions produce more toxicities and deaths. In the concurrent experiment cited the maleate salt was administered as a 1% solution, whereas the open ring compound was given as a 2% solution. (Personal communication with Dr. Pfitzer, Hoffmann La-Roche. Supporting data is presented on pages 142-143, volume 1.127).
- d) All animals survived at the dosages tested. Adverse signs were decreased motor activity and ataxia.
- e) All animals survived at the dosages tested. Adverse signs included muscle relaxation, salivation, ataxia, sedation, disoriented behavior, and emesis.

2. Venous Irritation Study in Rabbits after Injection of Midazolam Maleate or Diazepam

Procedure: New Zealand Rabbits (NZW) were infused for 1 minute into the marginal ear vein with midazolam maleate 1.0 ml (10 mg/ml H₂O), or diazepam 1.0 ml (5 mg/ml organic diluent), or 1 ml of diazepam diluent, or 1 ml of saline. Signs of vein irritation were recorded for 10 days following administration of drugs or vehicle.

Results and Conclusions:

Compound	Concentration mg/ml	Thrombosis	Edema	Erythema	
				Injection Site	Non-Inject. Site
Saline	-	0/10	0/10	0/10	0/10
Diluent for Diazepam	-	4/10	4/10	6/10	4/10
Diazepam (in Diazepam Diluent)	5	4/10	7/10	8/10	7/10
Midazolam (in Water)	10	2/20	9/20	15/20	15/20

Midazolam at twice the concentration of diazepam was found to show similar evidence of venous irritation as diazepam or its diluent. Propylene glycol, an ingredient (40% v/v) in the diazepam diluent may contribute to the venous injury (Can. Anaesth. Soc. J. 25: 50-52, 1978).

3. Venous Irritation Study in Rabbits after Injection of Midazolam Maleate or Pentobarbital

Procedure: Three male and three female NZW rabbits per group were administered by I.V. injection into the posterior marginal ear vein: a) midazolam maleate (formulation A) at doses of 0.1, 0.5, and 2.5 mg/kg; b) 20 mg/kg Nembutal; c) vehicle; d) saline; e) uninjected control. The injection volume for controls was 1 ml/kg which was equivalent to the volume used for the high dose midazolam group. All injections were given over a 2 minute period. Daily observations for adverse clinical signs and possible vein irritation were made for 2 weeks.

Results and Conclusions:

One animal at 0.1 mg/kg midazolam showed slight sedation and ataxia. At 0.5 mg/kg slight to moderate ataxia, slowed righting reflexes and slight to moderate sedation occurred. One female lost the righting reflex. Four rabbits at 2.5 mg/kg of midazolam and 4 rabbits receiving Nembutal promptly demonstrated hypnosis after injection. Additional responses included: sedation, loss of righting reflex, ataxia and eye twitching. All rabbits appeared normal within 1-3 hours after injection.

The injection sites of rabbits treated with midazolam remained essentially free of inflammation, edema, or ulceration, venous flow was preserved. One Nembutal-treated rabbit developed venous occlusion and three others exhibited slight erythema and edema of the ear.

4. Venous Irritation Study in Rabbits after Injection of Midazolam Hydrochloride or Pentobarbital

Procedure: Five NZW rabbits per sex per group were administered by I.V. injection midazolam base or Nembutal into the left ear vein and an equal volume of vehicle into the right ear vein according to the schedule:

Group I: midazolam HCl (5 mg/ml) at 0.7 mg/kg in 0.14 ml/kg.

Group II: midazolam HCl (2mg/ml) at 0.7 mg/kg in 0.35 ml/kg.

Group III: Nembutal in saline 3 mg/kg in 0.12 ml/kg

The total volume was administered in about 45 seconds. The observation period was 14 days.

Results and Conclusions: Slight erythema was observed in all groups. Venous congestion which was scored beginning on day 2 post-dosing in groups receiving midazolam and from day 1 in rabbits receiving Nembutal, showed the following distribution:

Group I - 4 midazolam sites, 2 vehicle sites;
 Group II - 1 midazolam, 1 vehicle site. Most of the congestion subsided by day 7. Edema, necrosis, or thrombosis were not observed in any group. It is concluded that midazolam base injectable produced slight irritation which was comparable to that produced by the vehicle.

5. Muscle Irritation Study in Rabbits after Injection of Midazolam Maleate

Procedure: Nine NZW rabbits were injected at separate sites into the sacrospinalis muscle with both high (1.0 ml) and lower (0.1 ml) doses of midazolam maleate (2.5 mg/ml as base equivalents). Three rabbits were each sacrificed after 34, 48, and 72 hours. The injection sites were grossly examined for swelling, edema, hemorrhage, and necrosis.

Results and Conclusions: Slight hemorrhage was observed at the 0.1 injection sites. The hemorrhage was more pronounced at the 1.0 ml injection site. Necrosis was found at 2 of the 0.1 ml sites and 4 of the 1.0 ml sites.

6. Muscle Irritation Study in Rabbits after Injection of Midazolam Hydrochloride

Procedure: Eleven NZW rabbits were each injected at separate sites into the sacrospinalis muscle with 0.1 and 1.0 ml of midazolam hydrochloride (5 mg/ml) and similar volumes of vehicle. Muscle tissue was examined grossly.

Findings:

Muscle Irritation (summary of observations at 24, 48 and 72 hours)^a

	Edema	Hemorrhage	Necrosis
Midazolam 0.1 ml	non-irritating	v. slight	well defined
Vehicle	non-irritating	v. slight	non-irritating
Midazolam 1.0 ml	v. slight	moderate	moderate
Vehicle	non-irritating	well-defined	non-irritating

• irritation when observed tended to be of the same intensity at all time points examined.

Conclusion: Dose-related muscle irritation appeared to be due to midazolam HCl. Similar results were found with the maleate salt.

7. Venous Irritation Study in Dogs after Injection of Midazolam Maleate

Procedure: Three beagle dogs were administered by I.V. injection 0.5 mg/kg (0.2 ml/kg) of midazolam maleate and another 3 dogs were injected with vehicle (0.2 ml/kg).

Results and Conclusions: Pharmacological effects of muscle relaxation, salivation, ataxia, loss of placing reflex, dazed and disoriented behavior, and sedation were reported after midazolam treatment. Head shaking and licking were observed in some placebo-treated dogs. No evidence of hemolysis or irritation was observed 24 hours post-dosing.

8. Venous Irritation Study in Dogs after Injection of Midazolam Hydrochloride

Procedure: Two male and two female beagle dogs were administered by I.V. injection 0.7 mg/kg (0.7 ml/kg) of midazolam hydrochloride or saline (0.7 ml/kg) over a period of 30 seconds. Blood was drawn prior to and at 1 minute post-dosing. A 10 day observation period followed.

Results and Conclusions: No evidence of hemolysis or venous irritation was observed for any dog. All midazolam-treated dogs exhibited decreased motor activity, dazed appearance and moderate ataxia shortly after dosing.

Pyramiding Dose Toxicity Study of Midazolam Maleate in Dogs after Intramuscular Injection

Test Compound: Midazolam maleate (Formulation A, 2.5 mg/ml as the base equivalent); lot no. C104037-01. Saline, lot no. C105928-01.

Number of Dogs: 2M and 2F for test compound and for placebo control

Initial Weight: 7-9.7 kg

Route: I.M. into the thigh muscle of the hind leg.

Dosage: Midazolam at 0.01 (0.025 mg/kg) and 0.03 (0.075 mg/kg) ml/kg on Wednesday and Friday of the first week. Then 0.1 (0.25 mg/kg) and 0.3 (0.75 mg/kg) ml/kg on Monday and Wednesday of the 2nd week.

Duration of Study: Fourteen days after the final dose

Parameters: The injection site was grossly examined for signs of irritation for 24 hours post dosing. Clinical signs and food consumption evaluated throughout study; hematology (Ht. Hg., total and differential WBC) seven days pre-treatment and 24 hours after the final dose; clinical chemistry (BUN, SGOT, SGPT, SAP, and glucose) at baseline, 24 hours after 0.1 ml/kg and 1, 7, 14 days after 0.3 ml/kg.

Results: Erythema was observed at the injection site in 1 dog receiving lowest dose 0.01 ml/kg. BUN was elevated 1 and 7 days after 0.1 and 0.3 ml/kg, respectively. Various elevations in SAP and glucose in both midazolam and placebo-treated dogs when compared to baseline values.

Conclusion: No consistent toxicity was observed in midazolam-treated dogs.

Subchronic Toxicity Studies of Midazolam

1. Rats (I.M.)

Study Number: 36063

Testing Laboratory: Hoffmann La-Roche, Nutley, New Jersey

Duration: 2 weeks

Test Compounds: a) Midazolam base (formulation B, Nutley), lot no. C114351-01; b) Vehicle, lot no. C 111770-01

Number of Rats: 12 CRCD rats/sex/group

Initial Body Weight: Males 250 g; Females 155 g.

Route of Administration: I.M. into the posterior muscles of both legs

Dosage Levels: Saline control, vehicle control, midazolam at 0.5, 1.6, 5.0mg/kg/day. All treatment groups received a volume of 1 ml/kg/day.

Parameters: Clinical signs and body weight (daily); food consumption (weekly); ophthalmic and neurological examination (pretreatment and at term); hematology (Ht, Hg, coagulation time, WBC (total and differential) pretreatment and term; serum chemistry (glucose, SAP, SGPT, SGOT, BUN, t. bilirubin, cholesterol, t. CPK, t. protein) at term; urinalysis (S.G., pH, glucose, albumin, ketones, bilirubin, blood, microscopic examination of sediment) overnight sample before term; gross pathology on all rats; organ weights (heart, lungs, liver, kidneys, spleen, brain, testes, ovaries, uterus, adrenals, thyroid (fixed), pituitary (fixed)); histopathology (organs from saline control and HD groups and muscle tissue from injection sites of all groups).

Results:

Body Weight: Slight reduction mean weight HDM (about 5%) when compared to saline control.

Food consumption: Various small reductions in food consumption for vehicle and drug treatment groups when compared to saline control.

Clinical Signs: Dose related transient pharmacological signs of CNS depression in drug-treated groups.

Gross Pathology: Dose-related increased incidence of hemorrhage at the injection sites in MD and HD rats.

Histopathology: Moderate to severe chronic active myositis in most rats from all drug-treated groups. This involved myodegeneration, myonecrosis, focal hemorrhage and mixed inflammatory cell infiltration. Slight myositis were also observed in 16/24 rats in the vehicle control and 5/24 rats in the saline control group.

Summary and Conclusion: Daily I.M. injections of midazolam for two weeks resulted in the expected pharmacological signs of CNS depression. All drug dosages tested caused focal active myositis which was more severe than that produced by the vehicle control. The lowest drug dosage tested, 0.5 mg/kg/day (roughly 6X the suggested human I.M. dose) produced the same kind of lesions at the injection sites but when compared to damage at higher dosages less tissue was involved.

It is concluded that midazolam administered to rats daily by I.M. injection for 2 weeks at dosages up to 60X the suggested human dose did not cause systemic toxicities. Repeated dosing, however, caused muscle damage at the injection sites. It is doubtful that a no effect level can be reached in protocols using multiple I.M. injections since even saline injections caused myositis in some rats.

2. Rats (I.V.)

Study Number: 94153

Testing Laboratory: Hoffmann-La Roche, Basle, Switzerland

Duration: 5 weeks

Test Compound: Midazolam base (Formulation C, Basle), lot no. PT 978817 22

Number of rats: 12 Fullensdorf albino/sex/group

Initial Body Weight: About 160 g

Route of Administration: I.V. into tail veins (Group IV, I.P. during the 5th week due to swollen veins)

Dosage Levels:

- Group I, control (saline 1.2 ml/kg)
- Group II, 1 mg/kg/day (0.2 ml/kg)
- Group III, 2.5 mg/kg/day (0.5 ml/kg)
- Group IV, 6 mg/kg/day (1.2 ml/kg)

Parameters: Clinical signs (daily); body weight (3-7X/Week); ophthalmic examination (Term); hematology 6 rats/sex/group (RBC, Hg, platelets, WBC and differential, reticulocytes-control and HD only) weeks 2 and 5. serum chemistry 6 rats/sex group (SGOT, SGPT, SAP, bilirubin, BUN, glucose, cholesterol, sodium, potassium) weeks 2 and 5, and total protein and electrophoresis at week 5; urinalysis 6 rats/sex/group (volume, SG, pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, nitrite) at weeks 2 and 5; organ weights (adrenals, brain, heart, pituitary, kidneys, liver, lungs, ovaries, prostate, spleen, testes, thyroid, uterus); histopathology 6 rats/sex/group I and IV.

Results:

Body weight: Slight decrease in mean body weight (< 10%) in MD and HD M when compared to control

Clinical signs: Sedation and ataxia (transient) and acute sensitivity to noise in HD group.

Hematology: Slight increase in WBC in some rats of various dosing groups including controls.

Serum chemistry: High SGOT and SGPT values in 1HDF at week 2 (i.e. >300 μ l vs. 30 μ l which is within the normal range). This F not examined in week 5 since alternating rats were examined at the 2 time periods. Slight reduction (5%) in total protein in HDM at week 5.

Gross Pathology: Not done,

Histopathology: Tail veins not examined

Summary and Conclusions:

Except for the expected pharmacological signs of midazolam no evidence of consistent systemic toxicity was observed after 5 weeks of treatment. The elevated WBC count in some rats of all groups was probably due to irritation of the tail tissue. All rats in the C, LD, MD were treated via the tail veins throughout the study; however, due to swollen veins most HD rats were administered midazolam by the I.P. route during the 5th week of the study.

3. Rabbits (I.V.)

Study Number: 30664

Testing Laboratory: Hoffmann-La Roche, Nutley, New Jersey

Duration: Two weeks

Test Compound: Midazolam Maleate (Formulation A)
lot number: 3 P2278
Placebo lot number: P3P-2280

Number of Rabbits: 4 NZW/sex/group

Initial Body Weight: Males 3.3 kg
Females 3.5 kg

Route of Administration: I.V. into the ear veins delivered between 45 seconds and 2 minutes

Dosage Levels: Midazolam base equivalent at 0.1, 0.5, and 2.5 mg/kg/day (injection volumes of 0.04, 0.2, and 1.0 ml/kg respectively). Placebo volume at 1.0 ml/kg. Injections were not given to a separate group of 8 rabbits.

Parameters: Clinical signs (daily); body weight (weekly); ophthalmic and neurologic examinations (pre-study and term); hematology (H_g, Ht, WBC total and differential, prothrombin and coagulation time) pre-study and term; serum chemistry (glucose, SAP, SGPT, SGOT, BUN) pre-study and term; urinalysis (S.G., pH, glucose, protein, ketones, bilirubin, blood, microscopic) pre-study and term; gross pathology; organ weights (heart, lungs, liver, kidney, spleen, brain, ovaries, testes, uterus, prostate, thyroid, adrenals, pituitary); histopathology.

Results:

Observed Effects:

Injection sites of rabbits for all groups showed focal venous occlusion, occasional clots and focal hemorrhages. Occasional extravasation and necrosis of tissue adjacent to the injection site were seen in high dose and placebo groups.

Hypnosis occurred at 2.5 mg/kg only. Sedation, loss of righting reflex, ataxia, muscular relaxation, rapid and shallow respiration and muscular twitching occurred at 2.5 and 0.5 mg/kg levels. Very slight sedation was noted at 0.1 mg/kg. These responses occurred in a dose-related manner that diminished somewhat in degree or duration over the treatment period.

Mortality:

One LD male after cardiac puncture for blood collection.

Body Weight:

Slight mean weight loss (6%) in the HD group. MD rabbits maintained their original weight, while LD and control rabbits showed a mean weight gain of 3-4%

Serum Chemistry:

Values were similar to control values except for a high average value for glucose in the high dose group, which was due to the elevation in a single male. Reason for this high individual value is not known. Also the mean BUN value was significantly lower for high dose group compared to control group.

Organ Weights:

In the HD rabbits the mean liver weight (absolute and relative) was decreased about 15% when compared to liver weight of placebo and uninjected controls.

Gross Pathology:

Principal changes were seen at the injection sites in the ears and thorax. In the ear, focal hemorrhage, soft tissue induration and necrosis were seen primarily in the high dose and placebo groups; lesser focal changes were seen in the mid and low dose groups. In some animals the heart and adjacent mediastinal and pulmonary tissues were the site of focal hemorrhage and inflammation consequent to repeated cardiac punctures.

Histopathology:

Focal lesions were seen at the injection sites that included thrombi in vessels, hemorrhage, focal necrosis about the site and ulceration of the skin. Extensive changes in the hearts of some animals were associated with cardiac puncture. Lesions in the lung included a focal arterial inflammation that was dose dependent but also occurred in two uninjected control animals. Special staining and observations of the pulmonary arteries did not show focal mural destruction or deformity of these arteries. Inflammatory lesions in the central nervous system occurred in 3 low dose, 2 mid dose, 1 high dose, 4 placebo and 3 uninjected controls.

Discussion:

The histological changes in the lungs of rabbits treated with midazolam was described as focal acute inflammation of branches of the pulmonary arteries. In some instances the change was localized to branches of the pulmonary arteries and included peribronchial lymphoid aggregates. In other cases the arterial inflammatory change was a part of interstitial pneumonia. In several other instances the arterial inflammation occurred in arteries not adjacent to lymphoid or inflammatory foci. In animals of the 0.1 mg/kg/day dose group, the vessels showing focal inflammatory change were small and these vessels were located peripherally in the lung. Examination of pulmonary vessels for emboli and thrombi revealed very few of these. One of the acute inflammatory foci surrounding an artery occurred within a hemorrhagic, peripheral pulmonic lesion having the configuration and character of an infarct, no thrombus was identified in this case. None of the arteries with focal acute inflammatory change showed any significant degree of mural destruction, deformity, or

obstruction of the lumen of the vessel. Elastic tissue stained sections of the lung confirmed the normal architectural arrangement of the elastic laminae of the arteries and in most areas the elastic elements of the alveolar walls. Similar arterial lesions were not observed in other organs or tissues of any rabbit.

The vascular inflammation appeared to be non-specific but could have resulted from:

- 1) emboli from the ear vein
- 2) direct drug induced toxic changes
- 3) hypersensitivity to the drug or drug-induced antigens
- 4) "spontaneous" vasculitis of unknown etiology

(The above are views expressed by the manufacturer's consultant, Dr. B.M. Wagner, Director of Laboratories, Overlook Hospital, Summit, New Jersey)

In order to investigate the vascular inflammation further, the following two additional rabbit studies number 29986 and 31955 were conducted.

Study Number: 29986

Testing Laboratory: Hoffmann-La Roche, Nutley, New Jersey

Duration: Two weeks of treatment; one half of the rabbits were sacrificed 2 weeks after last injection and the remaining rabbits were sacrificed 3 months after the final injection.

Test Compound: Midazolam Maleate (Formulation A)
lot number 3P-2328; placebo
lot number 3P-2279

Number of Rabbits: 12 NZH/group (all males except for 1 female at the 0.5 dose level)

Initial Body Weight: 3.3 kg

Route of Administration: I.V. into the marginal ear veins of alternative ears in the mornings of Monday, Wednesday, Friday of each week for 2 weeks.

Dosage Levels: Midazolam base equivalents at 0.1, 0.5, and 2.5 mg/kg (0.04, 0.2, and 1 ml/kg, respectively). Placebo vehicle at 1.0 ml/kg. Saline at 1.0 ml/kg. Nembutal at 20 mg/kg in a volume of 0.4 ml/kg/day. A noninjected control group.

Parameters: Clinical signs, irritation of tissue at the injection sites were observed daily for 32 days. Rabbits, with persistent ear changes were observed for 58 days. All other rabbits were examined weekly. Body weights were measured weekly. Gross pathology on all rabbits; one half 10-12 days after the last injection and the remaining rabbits at 3 months post-dosing. Organ weights (heart, lungs, liver, kidneys, spleen, brain, testes, prostate, ovaries, uterus, thyroid, adrenal, and pituitary). Histopathology on all rabbits.

Results:

Mortality: 3 rabbits, 1 vehicle control, 1 in the Nembutal group, and 1 in the HD midazolam group.

Observed Effects: Erythema and ecchymosis in areas of injection in some rabbits of all injected groups. Rabbits exhibiting venous occlusions were 4/12 in the HD midazolam group and 12/12 in the Nembutal group. Adverse responses at the injection site were also more severe with Nembutal than with midazolam, the former drug produced sloughing and scab formation, and an exudate was seen occasionally.

Pharmacological signs of ataxia, impaired righting reflexes, and sedation were observed in most rabbits after midazolam injection. These effects and their duration were slight in the LD group. Nembutal produced muscle relaxation, ataxia, abnormal eye movements and sedation. Vehicle, saline, and uninjected controls were asymptomatic.

Body Weight: Slight (less than 5%) decrease in HD midazolam group during the treatment period. A similar decrease from control values was observed for the Nembutal group during the first week of treatment.

Histopathology: At 10-12 days after the last injection 1/6 rabbits treated with midazolam had a thrombus in an ear vein while 2/5 Nembutal-treated rabbits showed ear vein thromboses, evidence of necrosis, inflammation and scar tissue.

At the 3 month sacrifice, no vascular lesions were found in the ears or any other organ.

A variety of random inflammatory lesions were noted in lungs, kidneys, liver, urinary bladder or brain of some rabbits in each group. There was no dose-response or indication that the histopathological lesions were related to midazolam or the other treatments used.

Evaluation: The results of this test indicate that the focal, pulmonary arteritis observed in study number 30664 is not midazolam related as regards direct drug toxicity or drug-related hypersensitivity.

Study Number: 31955

Testing Laboratory: Hoffman-La Roche, Nutley, New Jersey

Duration: Two weeks of treatment. All rabbits sacrificed nineteen weeks after the last injection.

Test Compound: Midazolam maleate (Formulation A), lot number 3 P-2328;

Vehicle lot number 3 P-2279

Number of Rabbits: 4 NZW/sex/group

Initial Body Weight: Males, 3.0 kg
Females, 3.2 kg

Route of

Administration: I.V. into the marginal ear veins of alternate ears daily for 2 weeks.

Dosage levels: Midazolam at 0.1, 0.5 and 2.5 mg/kg/day (0.04, 0.2, and 1.0 ml/kg, respectively); vehicle control at 1.0 ml/kg, respectively); vehicle control at 1.0 ml/kg, respectively); vehicle control at 1.0 ml/kg; saline control at 1.0 ml/kg; Nembutal at 20 mg/kg for 2 days then 15 mg/kg/day (0.3 ml/kg) for remaining treatment days. Uninjected controls.

Parameters: Clinical signs and tissue at injection sites (daily for first 30 days and then weekly); body weight (weekly); gross pathology of cervical, thoracic, abdominal organs, and of pituitary, brain and spinal cord; organ weight (heart, lungs, liver, prostate, thyroid, adrenals, pituitary); histopathology of lungs.

Results:

Mortality: Two Nembutal-treated rabbits

Clinical signs: Dose-related erythema and ecchymosis was observed at the injection site of treated rabbits. Venous occlusion occurred primarily in MD and HD midazolam groups and in the Nembutal group. Scar tissue and sloughing was noticed in 3/8 HD midazolam rabbits and in 6/6 rabbits treated with Nembutal. Sedation, loss of righting reflexes and abnormal eye movements were noted in the MD and HD midazolam rabbits. These effects were judged to be more severe in the Nembutal-treated group.

Body Weight: Dose-related decrease in body weight when compared to control in MD (6%) and HD (10%) groups during the 2 week treatment period. The body weight of Nembutal-treated rabbits was similar to control.

Histopathology: There were no drug-related changes in lungs of the rabbits in this study.

Discussion and Conclusion: A previous study (no. 30664) indicated focal arterial inflammatory changes in the lungs of rabbits after 2 weeks of I.V. injections of midazolam. An additional study (no. 29986) and the present study did not show evidence of drug induced pulmonary arteritis. The vasculitis, therefore, does not appear to be the result of direct drug toxicity or the result of hypersensitivity reactions to the drug. However, Dr. B.M. Wagner, the manufacturer's consultant states it is not possible to exclude the role of venous emboli from the injected ear veins as the cause for the lung arteritis observed in study no. 30664.

4. Dogs (I.M.)

Study Number: 35277

Testing Laboratory: Hoffmann-La Roche, Nutley, New Jersey

Duration: 2 weeks

Test Compounds: Midazolam (Formulation B, 5 mg/ml of base equivalents)
lot number C 114351-01
Vehicle, lot number C111770-01
Saline

Number of Dogs: 3 Beagles/sex/group

Initial Body Weights:
Males 8.2 kg
Females 8.1 kg

Route of Administration: I.M. injection into the posterior thigh muscle. The volume injected for the high dose, vehicle and saline groups was divided into two parts and injected into both hind legs each day.

Dosage Levels: Midazolam at 0.3, 1.0 and 3.0 mg/kg/day (0.06, 0.2, and 0.6 ml/kg, respectively). Vehicle and saline were administered at 0.6 ml/kg/day.

Parameters: Clinical signs (daily); body weight (weekly). Prestudy and term: neurological and ophthalmic examination; EKG; hematology (Ht, Hg, WBC total and differential, prothrombin and coagulation time) serum chemistry (glucose, SAP, SGOT, SGPT, BUN, total protein, total cholesterol, bilirubin, CPK); urinalysis (ph, S.G., glucose, albumin, ketones, bilirubin, blood, microscopic examination of sediment); gross pathology; organ weights (heart, lungs, liver, kidneys, spleen, brain, ovaries, testes, uterus, prostate, thyroid, adrenal, pituitary); histopathology (HD and saline-treated dogs plus prostate and testes and injection sites of all dogs).

Results:

Clinical signs: There were dose-related pharmacological signs in MD and HD dogs consisting of ataxia, decreased activity and dazed appearance which were transient and disappeared within 2 hours after dosing. A single instance of ataxia occurred in 1 LD dog. Behavioral changes, also dose-related, included unusual barking, nipping, and excitement. Most unusual behaviors occurred in MD and HD dogs but a few isolated instances also were observed in the low dose group.

Serum Chemistry: In the HD group mean creatinine phosphokinase levels were significantly increased (65% compared to control). Also SGPT levels were increased (75%) and SGOT (23%).

Organ weights: Absolute and relative testes weights were somewhat reduced (35%) in HD dogs without evidence of histopathological findings.

Gross pathology: Most dogs injected with drug or vehicle had edema and hemorrhage at the injection sites. Two saline-treated dogs were also affected.

Histopathology: At the injection sites, mild focal changes in the muscle consisting of necrosis, edema, hemorrhage, scarring and inflammatory cell infiltration were found in 5/6 HD, 3/6 MD, 4/6 LD, 2/6 vehicle control, and 4/6 dogs in the saline control group.

Summary and Conclusion:

The expected pharmacological signs common to benzodiazepine drugs were observed in this species. Clinical chemistry also showed elevated liver enzymes (SAP, SGPT) which are also characteristic responses in dogs to members of this drug class. The elevated serum CPK noted in the MD dogs probably resulted from local muscle damage caused by repeated injections of relatively large doses (35X the suggested human dose) of this drug.

5. Dog (I.V.)

Study Number: 30663

Testing Laboratories: Hoffmann La-Roche, Nutley, New Jersey

Duration: 2 weeks

Test Compound: Midazolam maleate (Formulation A),
lot number 3P-2278
Vehicle, lot number 3P-2280

Number of Dogs: 3 Beagles/sex/group

Average Body Weights: Males, 12.6 kg, Females 9.0 kg

Route of Administration: I.V. injections into the cephalic vein of alternative forelimbs

Dosage Levels: Midazolam at 0.1, 0.5, and 2.5 mg/kg/day (injection volumes of 0.04, 0.2, 1.0 ml/kg, respectively). Vehicle at 1.0 ml/kg. Uninjected controls.

Parameters: Clinical Signs (daily); body weights (weekly). Prior to and at end of study: Ophthalmic examination, hematology (Hb, Ht, WBC and differential, prothrombin and coagulation time); Clinical chemistry (glucose, SAP, SGOT, SGPT, BUN); urinalysis (S.G., pH, glucose, protein, ketones, bilirubin, blood, microscopic examination of urinary sediment). Gross pathology; organ weights (heart, lungs, liver, kidneys, spleen, brain, ovaries, testes, uterus, prostate, thyroid, adrenals, pituitary); histopathology.

Results:**Clinical signs:**

The injection sites were free of inflammation, edema or ulceration with the exception of slight transient edema of one high dose male on day 7 only.

At 0.1 mg/kg slight ataxia, hyperactivity, and a biting and chewing reaction was observed with onset occurring immediately after dosing and lasting up to 20 minutes.

At 0.5 mg/kg the above effects lasted up to 30 minutes. All 6 dogs exhibited muscular relaxation of the limbs and incoordination immediately after the first daily injection, but rarely thereafter. Occasional hyperactivity and prominence of small conjunctival blood vessels were noted in several animals.

At 2.5 mg/kg all of the above effects were observed plus sedation and occasional retching and emesis. Reactions usually lasted up to one hour after injection and diminished to an overall duration of no more than 30 minutes by the end of the second week of study.

Body weight:

At 2.5 mg/kg a slight decrease (0.1 kg) occurred over the 2 week treatment period.

Gross Pathology

Injection sites showed no detectable swelling or necrosis of overlying skin and soft tissue. Dissection of the site frequently revealed extravasation of blood.

Histopathology

Dose-related pathological venous changes including phlebitis, sclerosis, hyperplasia, thrombosis principally in MD and HD groups. Fibrosis was observed in LD and vehicle control groups.

Summary and Conclusion:

A two week intravenous study in dogs (0.1, 0.5 and 2.5 mg/kg) produced dose dependent transient effects, lasting up to an hour, consisting of altered behavior and neurologic function. Histologic observations revealed focal changes (hyperplasia, thrombosis, sclerosis and fibrosis) at the sites of repeated injection. These venous changes were dose-related and occurred primarily in dogs receiving injections of 0.5 mg/kg and 2.5 mg/kg. Venous changes (fibrosis) in the low dose group (0.1 mg/kg) were similar to changes found in dogs injected with the vehicle.

6. Dog (I.V. and I.M)

Study number: 94152

Testing laboratory: Hoffmann-La Roche, Basle, Switzerland

Duration: 5 weeks

Test Compound: Midazolam base (Formulation C),
lot number OP PT 9788 H22

Average Body Weights: Males 12.0-15.2 kg
(Swiss Beagle) Females 9.8-13.4 kg

Route of Administration: I.V. and I.M. (specific sites not given)

Dosage Levels:

Group	Midazolam mg/kg/day	Midazolam ml/kg/day		Dogs	
				M	F
I	0	1.2 saline	i.v.	3	3
II	1	0.2	i.v.	3	3
IIIa	2.5	0.5	i.v.	2	2
IIIb	2.5	0.5	i.m.	2	2
IV	6	1.2	i.v.	3	3

Parameters: Clinical signs and body weight (daily); hematology (RBC, Hg., WBC and differential reticulocytes, platelets) pretreatment, 2 and 5 weeks; serum chemistry (SGOT, SGPT, SAP, bilirubin, BUN, glucose, electrolytes, cholesterol; t. protein electrophoresis [0 and 5 weeks] pretreatment, 2 and 5 weeks; urinalysis (S.G., pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, nitrites, sediment) at 2 and 5 weeks; EKG (all groups week 0 and groups I and IV at week 5); organ weights (adrenals, brain, heart, pituitary, kidneys, liver, lungs, ovaries, prostate, spleen, testes, thyroid/parathyroid, uterus); histopathology.

Results:

Clinical Signs: Dose-dependent sedation, ataxia which diminished with time and duration of treatment. Mild effects in MD and LD dogs after 1 week of treatment.

Serum Chemistry: When compared to saline controls, there was a slight increase in SAP in most treated groups at 2 and 5 weeks. There was a slight increase in mean SGOT at week 2 in the group receiving 2.5 mg/kg by I.M. injection. One dog exhibited a large increase in SGPT (group Ia) at week 2 but this parameter was within normal limits at week 5.

Histopathology: Inflammation was observed at the I.M. injection sites of dogs receiving 2.5 mg/kg. One dog in this group also had focal myositis and necrosis. After repeated I.V. injections some dogs in all groups exhibited phlebitis and periphlebitis with hematomas. Drug-treated groups were affected more severely. The number of dogs affected were 2/6 controls, 3/6 LD, 2/4 MD and 6/6 HD. One HD dog (6 mg/kg) also had venous obliteration.

Summary and Evaluation:

The expected CNS pharmacological signs characteristic of benzodiazepine drugs were seen. No consistent systemic abnormalities were noted with the exception of transient and/or slight to moderate elevation in liver enzymes. Transient elevations of this type have been noted previously with other benzodiazepine drugs in dogs. The pathological changes observed were limited to the injection sites. Dose related myositis and muscle degeneration occurred after IM injections of midazolam and more severe phlebitis, periphlebitis and hematomas were observed in dogs injected I.V. with midazolam when compared to the saline-injected control dogs.

Reproduction Studies**J. Fertility and Reproduction Study in Rats (Segment I)****Study Number: 32713****Testing Laboratory: Hoffmann-LaRoche, Nutley, New Jersey****Test Compounds: Midazolam maleate (formulation A)
lot number C-10403701; vehicle lot number and C-1055801 and
C-10276701****Number of Rats: 24 male and 24 female CRCD rats/group****Initial Age: About 110 days old****Route of
Administration:**

Oral intubation (Note: Parenteral administration was considered impractical due to the long term dosing requirements of the Segment I reproduction study. The sponsor in a dose-finding study determined the oral doses of midazolam maleate injectable substance which could be satisfactory replacements for I.V. doses. It was found that 16 mg/kg orally produced similar clinical signs and blood levels (AUC) as did an I.V. dose of 4 mg/kg. On this basis, the high oral dose selected for the Segment I study was 16 mg/kg.

Dosage Levels:

Midazolam maleate at 1, 4, 16mg/kg/day in a volume of 6.4 ml/kg. Vehicle (formulation without midazolam) at 6.4 ml/kg/day.

Duration of treatment:

Males were treated for 62 days prior to mating and throughout the mating period (2 weeks). Females were dosed 14 days prior to mating and until sacrifice at day 13 of gestation (Group A-12 females) or until day 21 of lactation (Group B-12 females).

Parameters:

Male and female body weights initially and at weekly intervals. Females were also weighed on gestation day 0, 7, 14, and 21 and lactation days 0

(delivery), 7, 14, and 21 (weaning). On day 13 of gestation, the number of corpora lutea, embryos, and resorptions were recorded. The remaining dams (about 8-12 in each group) delivered their young at term and the litters were examined for live and still born offspring. The pups were examined for external malformations, counted and weighed at birth, and on day 4 and 21 of lactation. The study was terminated at weaning of the pups. The dams were examined for implantation sites, and 1/3 of each litter was examined for visceral malformations. The heart, liver and kidneys of these pups were also weighed.

Results and Summary:

Parental effects: Dose-related pharmacological signs which included ataxia. Similar effects were observed in both sexes. Average body weight of dams receiving the low dose (1 mg/kg/day) were slightly higher (6%) during the latter part of the lactational period.

Litter effects: Adverse effects were not noted on day 13 of gestation. A slight decrease (8%) in the mean relative heart weight was observed in high dose female pups when compared to controls but this was not significantly different when compared to low-dose female pups. This small difference is not likely to be biologically significant.

Conclusion:

Midazolam maleate injectable formulation administered by gavage to male and female rats at doses up to 16 mg/kg/day does not have adverse effects on reproduction parameters, pregnancy, or the offspring of these pregnancies.

2. Teratology Studies in Rats (Segment II)

Study Number: 31498

Testing Laboratory: Hoffmann-La Roche, Nutley, New Jersey

Testing Compounds: Midazolam maleate (formulation A)
lot no. C-100756-01.
Vehicle, lot no. C-10276701

Number of rats: 30 female Charles River CD rats/group
60 males (untreated)

Initial Age: Adult males, females about 110 days old

Route of Administration: I.V. into the caudal vein at a rate of about 2 ± 0.5 ml/min.

Dosage Levels: Midazolam maleate as the base equivalent at 0.2, 1.0 and 4.0 mg/kg/day in a volume of 1.6 ml/kg/day. Vehicle at 1.6 ml/kg/day. Untreated controls.

Duration of treatment:

Gestation days 7 through 15 (day 0 being the day a copulation plug was found). About 20 females per group for C-section on day 21. Ten females/group were allowed to deliver and wean their young.

Parameters:

All female body weights were recorded on days 0, 7, 11, 15, 21 of gestation. For groups that weaned their young, body weights were recorded on the day of parturition, day 7, 14 and 21 (weaning). Implantation, resorption sites, and corpora lutea were counted. Fetuses were weighed and examined for external abnormalities. About 1/3 were examined for soft tissue anomalies and the rest for skeletal malformations. For the group allowed to deliver, the litters were examined for external abnormalities, weighed individually at birth and on days 4, 14 and 21 of lactation. For statistical tests the litter was considered to be the unit of treatment.

Maternal Effects: All drug treated females showed slight to moderate ataxia lasting 15-30 minutes after injection. Decreased weight gain (about 5%) was recorded on days 11-15 in the high dose group when compared to control.

Fetal Effects: Teratology: no adverse drug related effects. There was a dose-related increase in post-implantation loss in pups from females allowed to deliver: vehicle control 4%, LD 9%, MD 12%, HD 16% (includes dead pups, resorbed fetuses and cannibalized pups). Note: Historical control (Segment I studies) indicated post-implantation losses over a range of 3-15%.

Summary of Results

Treatment groups (mg/kg)	Untreated Control	Vehicle	0.2	1.0	4.0
Pregnant rats at term (no.)	20	19	18	20	18
Viable fetuses (no.)	253	234	229	272	235
Average litter size (no.)	12.6 ± .6	12.3 ± .6	12.7 ± .7	13.6 ± .5	13.1 ± .7
Resorptions (%) (no. resorptions/ no. implantations)	7.3	6.0	6.9	6.2	7.8
External abnormalities (no.)	0	0	1	0	0
Visceral abnormalities (no.) (no. examined)	1 87	0 80	2 75	1 92	0 81
Skeletal abnormalities (no.) (no. examined)	0 166	0 154	0 154	0 180	0 154
Skeletal variations (no. examined)	53 166	53 154	51 154	50 180	56 154

Evaluation:

In the Segment II teratology study in rats there was no evidence of drug induced fetal abnormalities. The increase in post-implantation loss in litters allowed to deliver from the MD and HD groups does not appear drug related because losses were within the historical control incidence and dose-related post-implantation loss was not evident in the the teratology phase of this study.

3. Rabbit Teratology Study (Segment II)

Study Number: 31496

Testing Laboratory: Hoffmann-La-Roche, Nutley, New Jersey

Test Compounds: Midazolam maleate (formulation A)
lot no. C-100756-01.
Vehicle lot no. C-102767-01

Number of Rabbits: 15 females NZ/ per drug groups
30 females for vehicle control group
15 females for non-treated control group

Initial Weight: About 4.3 kg

Route of Administration:

I.V. into the ear vein at a rate approximately 2 ± 0.5 ml/minute

Dosage Levels: Midazolam maleate as the base equivalent at 0.2, 0.6 and 2.0 mg/kg/day; vehicle at 0.8 ml/kg/day.

Duration of Treatment:

Daily from day 7 to day 18 of gestation (day 0 being the first 24 hours after observed mating).

Parameters:

Observation of all females, 1 hour after dosing and at the time of weighing. Body weights reported for days 0, 7, 14, 21 and 29 of gestation. Viable fetuses, resorptions, and corpora lutea counted. All fetuses examined for external malformations, sexed, weighed and sized. Viable fetuses incubated for 24 hours to determine survivability. All pups examined for visceral and skeletal abnormalities. For statistical analysis the litter was considered the unit of treatment.

Maternal Effects: Dose-related ataxia and sedation. The low dose group was asymptomatic 60 minutes post-dosing. The mid dose group showed few effects and the high dose group showed marked effects even at 60 minutes after dosing. These signs were generally absent after two hours. Maternal body weight was not effected by drug treatment.

Fetal Effects: The resorption rate was greater in the high dose group (17.4%) but not statistically different when compared to other groups: -untreated control (11.2%), vehicle (10%), low dose (13.8%) and mid-dose (8.2%). A statistically significant increase in external abnormalities was found in the low-dose group, but without a specific syndrome of malformation and most (9) abnormal fetuses were from one litter. In this group, 9 litters of 13 showed no external abnormalities.

Treatment groups (mg/kg)	Summary of Results				
	Untreated Control	Vehicle	0.2	0.6	2.0
Pregnant rats of term (no.)	13	22	13	13	9
Viable fetuses (no.)	103	188	106	112	71
Average Litter Size (no.)	7.9 ± .5	8.5 ± .5	8.2 ± .8	8.6 ± .5	7.9 ± 1
Resorptions (%) (no. resorptions/ no. implantations)	11.2	10	13.8	8.2	17.4
External abnormalities (no.)	0	1	12*	0	0
Visceral abnormalities (no.)	0	4	2	4	1
Skeletal abnormalities (no.)	6	11	13	2	2
Abnormalities (%) (no.)	5.8 6/103	7.4 14/188	17.9 19/106	5.4 6/112	4.2 3/71

*1 fetus-hyperflexion of forepaws, 1 fetus-domeshaped head, 1 fetus pes cavus, 9 fetuses (one litter)-open eyelids, cleft palate.

Evaluation: Although dose-related pharmacological signs of maternal adverse effects were observed, there was no evidence of drug-related fetal malformations. The resorption rate in the high dose group, while greater than the incidence found in the other concurrent groups, is not outside the range for spontaneous resorptions in rabbits.

4. Prenatal/Postnatal Reproduction Study in Rats (Segment III)

Study Number: 32711

Testing Laboratory: Hoffmann-La Roche, Nutley, New Jersey

Test Compound: Midazolam maleate (formulation A)
lot. no. C-100756-01; Vehicle,
lot no. C-10276701 and C-105558-01

Number of rats: 20 female CRCD rats per dose group

Initial Age: About 100 days old

Route of Administration: I.V. into the caudal vein at a rate of about 2 ± 0.5 ml/minute.

Dosage Levels:

Midazolam maleate as the base equivalent at 0.2, 1.0 and 4.0 mg/kg/day in a volume of 1.6 ml/kg/day; vehicle at 1.6 ml/kg/day; non-treated controls.

Duration of Treatment: Day 15 of gestation (finding of vaginal plug was day 0) through day 21 of lactation.

Parameters:

Female body weights were recorded on gestation day 0 and 15 and on lactation days 0 (delivery), 7, 14, and 21. Litters were examined for live and dead offspring and external abnormalities. Then pups were weighed at birth and days 4 and 21. At day 21 about 1/3 of each litter was autopsied and weights of heart, kidneys and liver were recorded. Pups that died during the study were examined for skeletal abnormalities.

Maternal Effects:

Dose-related pharmacological effects of ataxia and transient voracious behavior immediately after dosing. Slight reduction in weight gain on lactation day 0 and day 7 in the high dose group. Also a statistically significant reduction in weight gain in the mid-dose group on lactation day 7.

Litter Effects:**Summary:**

Treatment groups (mg/kg)	Untreated Control	Vehicle	0.2	1.0	4.0
Litters born	17	19	17	18	18
Average litter size at birth	11.9 ± 0.6	13.4 ± 0.5	12.4 ± 0.6	12.4 ± 0.4	10.4 ± 0.9

Pups missing and presumed cannibalized	3	2	0	10	7
Lactation Index (pups alive day 21/pups at day 4)	100	98.7	100	100	100

Summary and Conclusions:

Dosages of midazolam that caused significant pharmacological effects in pregnant rats produced no consistent adverse effects in the offspring. The slight decrease from control in relative heart weight (7%) in the high dose male pups appears to correspond to the increased body weight gain of these pups. It is known that smaller litters generally weigh more than larger litters. There is no convincing evidence that the smaller litter size of the high dose group was directly related to midazolam.

Carcinogenicity Studies**1. Carcinogenicity Study in Mice**

Study Number: 35030 (Interim report)

Testing laboratory: International Research and Development Corporation
(IRDC)
Mattawan, Michigan

Duration: 24 months

Test Compound: Midazolam maleate (lot no. 0003003)

Number of Mice: 80 B₆C₃F₁/sex/group

Age at onset of dosing: About 5 weeks old, weight greater than 12 grams

Route of Administration: Mixed in food. Food analyzed for homogeneity at pretest, and weeks 1, 13, and then every 13 weeks.

Dosage Levels: Midazolam at 0, 0, 1, 9, 80 mg/kg/day

Parameters:

Clinical signs (daily with more detailed weekly observations such as masses, corneal opacities, incisor maladjustment); body weight and food consumption (weekly for the first 14 weeks, thereafter every two weeks); ophthalmoscopic examinations (pretest and at 3, 6, 12, 15, 18, 21, and 24 months); hematology: Hg, Ht, RBC, WBC, differential, platelets (in mice sacrificed at pretest, 18, and 24 months); gross pathology (all mice that died or were sacrificed); organ weights (brain, liver, kidneys, spleen and heart at 24 months); histopathology: report not completed: results reported for most organs examined at 0-18 and 18 month interim sacrifice, whereas results from only the liver have been reported for mice that died or were sacrificed at 18-24 months.

Results:

Body Weight

Higher body weight gain for mid-dose and high-dose females (mean increase from controls of about 5% and 8%, respectively).

Survival at 104 Weeks

Dose (mg/kg/day)	No. survivors/no. initiated*	
	M	F
0	57/65	50/65
0	54/65	54/66
1	50/65	52/65
9	53/65	52/65
80	38/65	55/65

* Does not include the 18 month interim sacrifice of 15 mice/sex/group

Organ Weight

A statistically significant increase was observed in mean absolute and relative liver weight of the high dose female group and the mid and high dose males.

Gross Pathology

At about 70 weeks an increased number of high dose males had a single ventral abdominal mass. This was determined to be distended urinary bladders and ureters. Since most of these mice also had inflammation and ulceration of the prepuce, the distended bladders and ureters were considered secondary to the preputial inflammation.

Liver Mass/Nodules

Dose (mg/kg)	M		F	
	(DOS)	(TS)	(DOS)	(TS)
0	2	19	2	6
0	4	18	1	8
1	4	15	1	8
9	4	20	4	10
80	7	20	6	43*

DOS - 18 to 24 months
 TS - Term (24 month sacrifice)

Histopathology

A. Primary Liver Tumors (Adenomas and Carcinomas¹)

Dose (mg/kg)	Female Mice (B ₆ C ₃ F ₁)				
	0	0	1	9	80
0-18 Months					
No. of mice	20	22	15	19	17
No with tumors (%)	1 (5)	1 (5)	2 (13)	2 (11)	8 (47) ²
Adenoma	1		2	2	5
Carcinoma		1			3
18-24 Months					
No. of mice	60	58	65	61	63
No. with tumors (%)	4 (7)	5 (9)	10 (15)	9 (15)	50 (79) ²
Adenoma		2	9	5	26
Carcinoma	4	3	1	4	19

Overall Incidence

No. of mice	80	80	80	80	80
No. with tumors (%)	5 (6)	6 (8)	12 (15)	11 (14)	58 (73) ²
Adenomas	1	3	11	7	33
Carcinoma	4	3	1	4	25

- 1) A few hemangiomas also observed with no dose relationship.
- 2) Statistically increased from control. Also higher than historical controls for this strain of mouse.

Male Mice (B₆C₃F₁)

Dose (mg/kg)	0	0	1	9	80

0-18 Months

No. of mice	18	18	19	20	25
No. with tumors (%)	6 (33)	1 (6)	1 (5)	5 (25)	8 (32)
Adenoma	5		1	4	7
Carcinoma	1	1		1	1

18-24 Months

No. of Mice	62	62	61	60	55
No. with tumors (%)	24 (39)	30 (48)	20 (33)	24 (40)	28 (51)
Adenoma	14	15	9	6	12
Carcinoma	10	15	11	18	16

Overall Incidence

No. of mice	80	80	80	80	80
No. with tumors (%)	30 (38)	31 (39)	21 (26)	29 (36)	36 (45)
Adenomas	19	15	10	10	19
Carcinoma	11	16	11	18	17

Historical Control (Adenoma and Carcinoma (2 year studies))

	<u>M</u>	<u>F</u>
IRDC (1982)		3.3-4.3% (1,663 mice)
JNCI 62: 957 (1979)	16%	3%
JNCI 66: 1,175 (1981)	7-58% ¹	0-21% ¹
Chu/NIH NCI	20%	4%

¹ Range from 5 laboratories

Description of primary liver tumors in the present study:

Adenoma: Benign neoplasm characterized by proliferating homogenous cells most of which have well-defined borders. The cells are generally well-differentiated. Many tumors show focal to generalized fatty degeneration.

Carcinoma: Often massive in size with ill-defined borders. Contain large round cells with large hyperchromatic nuclei and a low mitotic index. Some tumors display a trabecular pattern with sinusoidal dilatation and large mononuclear giant cells having hyperchromatic nuclei. These cells were found in clusters and often separated from the major mass.

B. Hepatocellular Hypertrophy

Dose (mg/kg)	Female Mice				
	0	0	1	9	80
<u>0-18 Months</u>					
No. of mice	20	22	15	19	17
No. with hypertrophy(%)	0	0	0	1 (5)	7 (41)
No. with tumors				1	7
No. without tumors				1	7
<u>18-24 Months</u>					
No. of Mice	60	58	65	61	63
No with hypertrophy(%)	0	2 (3)	0	1 (2)	32 (51)
No. with tumors					22
No. without tumors		2		1	10
<u>Overall Incidence</u>					
No. of mice	80	80	80	80	80
No with hypertrophy(%)	0	2 (3)	0	2 (3)	39 (49)
No. with tumors					22
No. without tumors		2		2	17

Dose (mg/kg)	Male Mice				
	0	0	1	9	80
<u>0-18 Months</u>					
No. of mice	18	18	19	20	25
No. with hypertrophy (%)	0	1 (6)	0	0	18 (72)
No. with tumors ¹					3
No. without tumors		1			15
<u>18-24 Months</u>					
No. of Mice	62	62	61	60	55
No. with hypertrophy (%)	3 (5)	3 (5)	5 (8)	8 (13)	39 (71)
No. with tumors ¹					19
No. without tumors	3	3	5	8	20
<u>Overall Incidence</u>					
No. of mice	80	80	80	80	80
No. with hypertrophy (%)	3 (4)	4 (5)	5 (6)	8 (10)	57 (71)
No. with tumors ¹					22
No. without tumors	3	4	5	8	35

¹ Adenomas or carcinomas plus hypertrophy

Evaluation:

There is an increased incidence of primary liver tumors (adenomas and carcinomas) in female mice that received the high dose of 80 mg/kg/day. The increase in liver tumors is statistically significant at 18 months or longer when compared to the incidence of tumors in control female mice.

2. Carcinogenicity Study in Rats

Study Number: 35278 (Interim report, volumes 13.1 and 13.3)

Testing Laboratory: Hoffmann-LaRoche, Nutley, New Jersey

Duration: Two year oral toxicity/carcinogenicity study. (Interim report 78 weeks)

Test Compound: Midazolam maleate (lot nos. 0003001, 009011, 010071, 007110, and 0009004)

No. of rats: 90 CRSD/sex/group

Age at Onset of Dosing: 4-5 weeks old, 86 gm. males and 80 g females

Route of Administration: Mixed in food, diets were prepared weekly.

Dosage Levels: Midazolam at 0, 0, 1, 9, 80 mg/kg/day.

Parameters:

Mortality and morbidity (daily); clinical signs, body weight, food consumption (weekly); neurological examination (pre-dosing then at quarterly intervals); ophthalmologic examination (all rats pre-dosing and 10/sex/group at weeks 14, 26, 39, 52, 67, 15 sex/group at week 77); hematology: Hg, Ht, WBC and differential, coagulation time (10 rats/sex/group pre-dosing and at 11, 26, 39, 51, 66 weeks; 15/sex/group after 77 weeks); serum chemistry: glucose, SAP, SGOT, SGPT, BUN (at sacrifice); serum prolactin (rats sacrificed after 78 weeks); urinalysis: color, SG, pH, glucose, albumin, ketones, bilirubin, blood, sediment on 10/sex/group at weeks 11, 26, 39, 51, 66 and on 15 sex/group after 78 weeks); pathology: all rats that died, 10 sex/group after 26 weeks and 15/sex/group after 78 weeks); organ weights: heart, lung, liver, kidneys, adrenals, spleen, brain, testes, ovaries, uterus, thyroid (fixed), and pituitary (fixed); histopathology: the interim reports give a summary of liver histology at term (2 years). Appendix A, volume 13.1.

Results:

Mortality: (by week 78, excluding interim sacrifice on week 26 of 10/sex/group, and on week 78 of 15/sex/group).

Dose (mg/kg)	M	F
0	5	6
0.2	10	4
1	11	9
9	7	6
80	15	9

Body Weight

When compared to controls, high dose male body weight was slightly higher (less than 10%) from weeks 11-50; thereafter, the body weight was slightly lower (less than 10%) from weeks 71 to week 78.

High dose female body weight gain was slightly lower from weeks 7-30 and then moderately lower (20%) from weeks 50-78.

Food Consumption

Consistently higher mean food consumption (about 5-10%) in high dose males from weeks 4-78.

Serum Chemistry

BUN: Slightly increased in high dose females at 26 weeks. Two HDM (BUN: 83.2 mg/dl, 92.4 mg/dl) and 2 HDF (82.4 ng/dl and 52.5 mg/dl) were examined at 78 weeks. Histopathology showed age-related kidney changes common to this strain.

Prolactin: Mean levels were lower in HDF (65 ng/ml versus about 100 ng/ml for other groups). All female rats with higher prolactin levels 125-500 ng/ml had pituitary tumors. However, pituitary tumors were also observed in some male and female rats with prolactin levels in the normal range. No dose relationship was evident for pituitary tumors.

Urinalysis

High dose male rats had increased excretion of albumin after weeks 26, 51, 66 and 78.

Organ WeightsRelative to Control

Liver: HDM increased absolute (54%) and relative weight (46%) at week 26 and 25% and 40%, respectively, at week 78.

HDF increased absolute (38%) and relative weight (33%) at 26 weeks and 20% and 33%, respectively, at 78 weeks.

Thyroid: HDM increased absolute (25%) and relative weight (15%) at 26 weeks and 40% and 57%, respectively at 78 weeks.

HDF increased absolute (8%) and relative weight (11%) at 26 weeks and 14% and 22%, respectively, at 78 weeks.

Histopathology

Liver:

Centrilobular Hypertrophy

26 weeks	78 weeks
A11 MDM + HDF	15/15 MDM
17/20 MDM + F	12/15 HDF
	7/15 MDM
	7/15 HDF
	3/15 LDF
	1/15 LDM
	0/30 C

A. Primary Liver Tumors (adenoma and carcinoma)

Dose (mg/kg)	Female Rats				
	0	0	1	9	80
<u>0-18 Months</u>					
No. of rats	31	29	34	31	34
No. with tumors (%)	0	2 (7)	1 (3)	3 (10)	1 (3)
Adenoma		2	1	1	
Carcinoma				2	1
<u>18-24 Months</u>					
No. of rats	59	61	56	59	56
No. with tumors (%)	2 (3)	1 (2)	4 (7)	3 (5)	7 (13)
Adenoma	2	1	4	2	6
Carcinoma				1	1
<u>Overall Incidence</u>					
No. of rats	90	90	90	90	90
No. with tumors (%)	2 (2)	3 (3)	5 (6)	6 (7)	8 (9)
Adenomas	2	3	5	3	6
Carcinoma		1		3	2

Dose (mg/kg)	Male Rats				
	0	0	1	9	80
0-18 Months					
No. of rats	30	35	35	32	40
No. with tumors (%)	2 (7)	3 (9)	0	0	1 (3)
Adenoma	1	3			1
Carcinoma	1				1
18-24 Months					
No. of rats	60	55	55	58	50
No. with tumors (%)	3 (5)	7 (13)	2 (4)	3 (5)	2 (4)
Adenoma	2	4	2	2	2
Carcinoma	1	3		1	
Overall Incidence					
No. of rats	90	90	90	90	90
No. with tumors (%)	5 (6)	10 (11)	2 (2)	3 (3)	3 (3)
Adenomas	3	7	2	2	1
Carcinoma	2	3		1	2

B. Non-Neoplastic Liver Histopathology: Female Rats

Dose (mg/kg)	0	0	1	9	80	
0-18 Months						
No. of rats		31	29	34	31	34
No. hyaline hyperplasia ¹		3	2	4	4	2
Clear cell hyperplasia ¹				1		4
Centrilobular hypertrophy				3	16	31
Centrilobular fatty change					1	1
18-24 Months						
No. of rats		59	61	56	59	56
No. hyaline hyperplasia		17	21	22	17	22
Clear cell hyperplasia		9	4	2	9	13
Centrilobular hypertrophy				3	20	47
Centrilobular fatty change					1	13

N 18654 -2 2

Overall Incidence

No. of rats	90	90	90	90	90
No. hyaline hyperplasia	20	23	26	21	24
Clear cell hyperplasia	9	4	3	9	17
Centrilobular hypertrophy			6	36	78
Centrilobular fatty change				2	14

¹ Modular hyperplasia either focal or multifocal

Non Neoplastic Liver Histopathology: Male Rats

Dose (mg/kg) 0 0 1 9 80

0-18 Months

No. of rats	30	35	35	32	40
No. hyaline hyperplasia ¹	4	5	2	6	2
Clear cell hyperplasia ¹	1				1
Centrilobular hyperplasia			1	19	33
Centrilobular fatty change			1		8

18-24 Months

No. of rats	60	55	55	58	50
No. hyaline hyperplasia	15	17	20	26	14
Clear cell hyperplasia	8	6	3	3	7
Centrilobular hypertrophy				31	39
Centrilobular fatty change		1		9	8

Overall Incidence

No. of rats	90	90	90	90	90
No. hyaline hyperplasia	19	22	22	32	16
Clear cell hyperplasia	9	6	3	3	8
Centrilobular hypertrophy			1	50	72
Centrilobular fatty change		1	1	9	16

Kidney: (0-18 months)

Focal Tubular Dilatation of the Cortex

Dose (mg/kg)	0		0		1		9		80	
	M	F	M	F	M	F	M	F	M	F
Number of rats affected	10/30	6/31	16/34	6/29	16/35	12/33	19/32	10/30	24/40	18/34
(%)	(33)	(19)	(47)	(21)	(46)	(36)	(59)	(33)	(60)	(56)

Evaluation:

This interim report contains the histopathological analysis of the liver after two years of continuous oral treatment with midazolam at doses of 1, 9, 80 mg/kg. Results from all other parameters are reported up to the 18 month interim sacrifice. Because the study report is not complete, only an evaluation of the liver will be made.

High dose rats, males and females, display drug-related hypertrophy and fatty changes in the centrilobular region of the liver. Primary liver tumors, adenomas and carcinomas, were not increased in male or female rats after 2 years treatment with midazolam.

Mutagenicity Studies**1. Bacteria**

Study Number: 89020

Test Compound: Midazolam maleate dissolved in distilled water

- a) Salmonella typhimurium: TA 1535, TA 1537, TA 1538, TA 98, and TA 100 with and without liver homogenate S-9 fraction prepared from male rats given 0.1% phenobarbitone in drinking water 5 days before sacrifice. Positive mutagens were not tested. (Standard Ames test).
- b) Fluctuation test: S. typhimurium, TA 1535, TA 1537 and TA 1538. Neither liver S-9 nor positive mutagenic compound were used.

Summary and Conclusions

Ames test: Midazolam maleate at concentrations of 0, 50, 100 and 500 ug/plate did not have mutagenic activity. At 750 ug/plate the test compound was toxic to the bacteria.

Fluctuation test: This test which can detect very weak mutagens (Mutation Research 65: 133-226 (1979)) did not reveal mutagenic activity for midazolam maleate at concentrations up to 25 ug/ml. Higher concentrations were toxic to the bacteria.

2. Bacteria

Study Number: 122616

Test Compounds: Midazolam maleate at 0, 2, 25, and 250 ug/plate with and without S-9 liver supernatant from B6C3F₁ female mice 42 days old administered midazolam 80/mg/kg/day in the diet for 8 days. Standard food without drug was given 18 hours before sacrifice. Aroclor-induced rat liver S-9 was used with known mutagens cyclophosphamide and benzopyrene.

Test bacterial strains: S. typhimurium TA 1535, TA 100, TA 1537, and TA 98 (Standard Ames test)

Results and Conclusions:

Midazolam at 250 ug/plate was at the limit of toxicity for TA 100. Therefore another experiment was conducted with 75, 150 and 200 ug/plate with TA 100. Midazolam with and without mouse liver S-9 did not exhibit mutagenic activity. The positive mutagens, cyclophosphamide and benzopyrene were mutagenic after rat S-9 activation in TA 1535, TA 100, TA 1537, and TA 98.

3. Mammalian Cells

Study Number: 96734 (Hoffmann-La Roche, Basle)

Test Compounds: Midazolam maleate in DMSO for 16 hours at 37.5, 75, 150 ug/ml without rat S-9 and for 5 hours at 37.5, 75, 150, 200, and 250 ug/ml with Aroclor-induced rat S-9. Positive controls were ethyl methanesulfonate and 2-acetyl-aminofluorene.

Test System: Chinese hamster lung cells (V79)

Results:

Incubation of cells for 16 hours with 37.5-150 mg/ml of midazolam without S-9 or for 5 hours with S-9 at 37.5-250 ug/ml did not induce mutations. Midazolam was found to be cytotoxic (cell survival 38%) at 150 ug/ml for 16 hours and at 250 ug/ml + S9 (27% cell survival). Positive mutagens induced point mutations as expected, i.e., forward mutations at the HGPRT locus resulting in 8-azaguanine resistant cells.

4. Human Lymphocytes

Study Number: 96684 (Hoffmann-La Roche, Basle)

Test Compounds and Procedures:

Midazolam maleate in saline at 10, 50, 100 ug/ml with Aroclor-induced rat liver S9 and at 5, 25, 50 ug/ml without S-9. Incubation times were two hours with S-9 and 24 hours without S-9. Positive mutagens were bleomycin sulfate 10 ug/ml in saline and cyclophosphamide (+S9) 50 ug/ml in water. The lymphocytes were prepared from a healthy 48 year old woman. A total of about 200 metaphases were scored (blinded) from each dose level.

Results:

There was no increase in chromosomal aberrations or breaks with midazolam. An increase in chromosome breaks was observed with the known mutagenic compounds.

5. Micronucleus Test in Mice (Fullensdorf Albino SPF, outbred strain, 6-8 weeks old).

Study Number: 96683 (Hoffmann-La Roche, Basle)

Test Compounds:

Midazolam maleate orally in saline at 0 (saline), 20, 400, 800 mg/kg. Procarbazine HCl was the positive control at 50 mg/kg.

Procedure:

Mice were orally administered compounds 30 and 6 hours before sacrifice of 3 males and 3 females/dose group. Four bone marrow smears were prepared from each mouse. About 2000 polychromatic erythrocytes were examined in a double blinded fashion.

Results:

Midazolam did not induce an increase in the number of micronuclei in PCE. Procarbazine caused an increase in the number of PCE micronuclei. Thus, midazolam did not produce chromosomal breaks or cause mitotic nondisjunctions under conditions of this experiment.

General Summary and Evaluation

Midazolam, an imidazobenzodiazepine, is a new chemical entity of the benzodiazepine class. Like all benzodiazepine drugs, midazolam's preclinical neuropharmacological profile demonstrates anxiolytic (anticonflict, calming effects), sedative, anticonvulsant, and muscle relaxant properties. Its range of activities, potency, and duration of action in various animal tests appears to be roughly similar to diazepam. It has high affinity in vitro for the benzodiazepine receptor in rat brain. Since midazolam salts are water soluble, its parenteral formulations are in aqueous media in contrast to currently available parenteral benzodiazepines which are soluble only in organic solvents. Hence, the parenteral form of midazolam was developed in anticipation that it would be more compatible and less irritating to tissues than other benzodiazepine drugs that require organic solvents for dissolution.

Metabolism and pharmacokinetic studies were conducted with ¹⁴C - labeled midazolam administered as a single I.V. dose to mice, rats, dogs and men. The major metabolite in all four species is the 1-hydroxymethyl compound with lesser amounts of the 4-hydroxy and the 1-hydroxymethyl-4-hydroxy analogs. Very little of the intact drug is excreted and virtually all of the metabolites in the urine are conjugated with glucuronide or sulfate. Pharmacological studies on mice indicated that the CNS activities are due to midazolam and not its metabolites. Dogs and men show a similar pharmacokinetic pattern after I.V. dosing. The elimination half-life in dogs and men is 1 and 1-2 hours, respectively. Recovery of 1-hydroxymethyl midazolam in the urine by 72 hours was about 40% of the administered dose for dogs and 40-60% for men. Placental transfer of ¹⁴C-midazolam occurs in rats; however, fetal levels of radioactivity were less than levels in maternal blood or in the placenta, which suggests slower or limited placental transfer of midazolam or its metabolites. Midazolam is highly bound (greater than 98%) in vitro to rat, dog, human plasma samples and to a human albumin solution.

Cardiovascular and respiratory parameters were measured after a single I.V. dose (range 4-20 mg/kg) of midazolam in barbiturate or chloral hydrate anesthetized dogs. Transient decreases were noted in blood pressure (25-40 mm Hg) and in the volume of inspired air (30%). Effects were not observed on myocardial performance or on ECG evaluations. Drug interaction studies were also conducted in conscious dogs administered an I.V. dose (0.15 mg/kg) of midazolam maleate alone or in combination with I.M. doses of hydroxyzine HCl (0.7 mg/kg), atropine sulfate (0.007 mg/kg) and meperidine HCl (1 mg/kg). There were slight transient decreases in blood pressure with the combination of hydroxyzine, atropine and meperidine and transient increases in blood pressure (20-30 mm Hg) with these three drugs plus midazolam or with midazolam and saline. After midazolam treatment, blood pressure returned to normal within 15 minutes.

Toxicological studies with midazolam include multi-week parenteral dosing in rats (2 weeks), rabbits (2 weeks) and dogs (2 and 5 weeks). The expected CNS pharmacological signs characteristic of benzodiazepine drugs were seen in all species. No consistent systemic abnormalities were noted with the exception of transient and/or slight to moderate elevation in liver enzymes SGPT, SGOT, and SAP in dogs. Transient elevation of serum transaminases and SAP have been noted previously with diazepam and other benzodiazepine drugs in dogs. In all species, midazolam formulation I.M. caused more severe myositis and muscle degeneration when compared to I.M. injections of vehicle or saline. Increases in serum CPK were also seen in dogs treated with high doses of midazolam (3 mg/kg for 2 weeks) and probably reflect the muscle damage seen. After I.V. injections of midazolam formulation in dogs for 5 weeks, more severe phlebitis, periphlebitis, hematomas were also observed when compared to vehicle or saline treated dogs. Thus, repeated I.M. or I.V. injections for two weeks or more with midazolam formulations causes greater muscle or venous pathology in dogs than vehicle or saline injections.

Reproduction studies were conducted in Charles River Sprague-Dawley rats and New Zealand White rabbits. A parenteral formulation of midazolam was administered by gavage in the segment I study in rats because long term I.V. or I.M. dosing is not possible due to the probable severe local irritation in this species. The high dose was 16 mg/kg/day which was selected because as a single oral dose it produces a similar time course of blood levels as a single I.V. dose of 4 mg/kg. Blood levels after multi-dose treatment were not determined. The results of this study showed dose-related parental ataxia without evidence of adverse effects on male or female fertility or general reproduction performance. The segment II or teratology studies were conducted in rats and rabbits administered the midazolam maleate formulation intravenously. The high dose in rats and rabbits was 4 mg/kg/day and 2 mg/kg/day, respectively. These dosages produced slight to moderate maternal ataxia and sedation without evidence of drug-related teratogenesis. A segment III perinatal and postnatal study in rats employed the midazolam maleate formulation administered intravenously at doses up to 4 mg/kg/day. Dose-related pharmacological signs were observed in female rats without evidence of adverse effects on the offspring.

Two year carcinogenicity studies were performed in B6C3F1 mice and Charles River Sprague Dawley rats with dietary doses of midazolam maleate up to 80 mg/kg/day. Preliminary reports of these studies have been submitted and contain complete histopathological evaluations of the liver. Data regarding all of the other organs under study have not been received. Recently, however, we received a statement about thyroid histopathology which indicated a two-fold increase in follicular tumors in male rats treated at the high dose (Submission April 20, 1984). An evaluation of this will be deferred until we receive the final reports of the carcinogenicity studies in mice and rats which are expected within a few months. In the meantime the following data appear relevant.

An increased incidence of primary liver tumors, adenomas and carcinomas, was observed in high dose female mice. The increase was statistically significant by 18 months (47% versus 5% in control female mice) and between 18 months to 2 years (79% versus 8% in controls). The increased incidence in midazolam treated females is much greater than reported for the laboratory control (3-4%) and in the literature for spontaneously occurring tumors in female B6C3F1 mice (0-21%); JNCI 62: 957, 1979 and JNCI 66: 1175, 1981). The incidence of liver tumors in male mice treated with the high dose of midazolam (45%) is not remarkably different from the incidence in the concurrent male controls (38%) and it is within the range for spontaneous tumors in males of this strain (7-58%; JNCI 66: 1175, 1981). Primary liver tumors were not increased in male or female rats treated for 2 years with the same doses of midazolam on an mg/kg basis.

The sponsor suggests that the liver tumors in female mice were secondary to liver cell hypertrophy which was induced by long term treatment with high doses of midazolam. They cite the experience with phenobarbital as an example of a liver enzyme inducer and an agent that causes liver hypertrophy and tumors in male and female CFI mice. (IARC monograph 13, 1977). The overall incidence of liver hypertrophy in high dose male mice was 71% (tumors incidence of 45%) while the incidence of hypertrophy for high dose female mice was 49% (tumor incidence of 73%). A greater number of high dose male mice died before 24 months which may account for the seemingly lack of correlation between tumors and hypertrophy. A more complete evaluation of the final report when it is received may shed light on this issue. Among currently marketed benzodiazepine drugs, there is evidence from a single study that oxazepam at high dietary doses induces a high incidence (75%) of liver tumors in male and female Swiss Webster mice (Res. Comm. Path. Pharm. 8: 481-488, 1974). Overall comparisons, with respect to animal liver tumors are not possible for all members of this class because while some drugs do not increase the incidence of tumors in rats and mice, several other drugs have rat but not mouse carcinogenicity studies, and a few of the drugs do not have adequate studies in either rats or mice (Pharmacology reviews 5/13/80 and 12/81; NDA 13-263). All new drugs of this class are expected to have rat and mouse carcinogenicity studies and oxazepam and chlordiazepoxide have ongoing rat carcinogenicity studies. For midazolam, mutagenicity tests in *Salmonella typhimurium* (TA 1535, 1537, 1538, 98, and 100), Chinese hamster lung cells (V79), human lymphocytes, and the micronucleus assay in mice did not show evidence of mutagenic activity. The lack of effect in mutagenicity tests and the fact that only female mice treated with high doses of midazolam developed tumors lends support to the idea of an initial epigenetic mechanism (e.g., sex hormone imbalances; Cancer Res. 36: 2584-2588, 1976) as opposed to a mechanism involving genetic mutations. Tumors that result from an obligatory initial epigenetic mechanism may be more likely associated with treatment of high drug dosages for long periods of time. These conditions do not apply to the proposed uses of the parenteral form of midazolam.

Recommendations:

1 The preclinical pharmacological and toxicological properties of the parenteral form of midazolam have been sufficiently characterized to support its approval for the proposed indications.

2 Labeling:**Carcinogenesis, mutagenesis, impairment of fertility**

Two year oral carcinogenicity studies in mice and rats with midazolam maleate at dosages up to 80 mg/kg/day have been conducted and analysis of the data is in progress. Histopathological evaluation of the liver tissue has been completed and shows an increased incidence of liver adenomas and carcinomas in female mice receiving the highest dosage level. The incidence of liver tumors in male mice was not remarkably different from the incidence in the concurrent controls or in the historical control for this strain of mouse. Liver tumors were not increased after midazolam treatment in male or female rats.

Midazolam did not have mutagenic activity in *Salmonella typhimurium* (5 bacterial strains), Chinese hamster lung cells (V79), human lymphocytes, or in the micronucleus test in mice.

A reproduction study in male and female rats did not show impairment of fertility.

Pregnancy: Teratogenic effects: Pregnancy Category D. See "Warnings" section.

Usage in Pregnancy:

Midazolam may cause fetal harm when administered to a pregnant woman. An increased risk of congenital malformations associated with the use of diazepam and chlordiazepoxide have been suggested in several studies. Teratology studies with midazolam in rats and rabbits at I.V. doses up to about 10X the human dose of 0.35 mg/kg did not induce malformations. Nevertheless, because of the human data with other benzodiazepines, if midazolam is used in pregnancy or the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Nonteratogenic effects:

Midazolam has not been evaluated in obstetrics. Transplacental distribution of other benzodiazepines, however, has occurred during the last weeks of pregnancy and has resulted in neonatal CNS depression. In animal studies, midazolam crosses the placenta in both rats and sheep although studies in rats have not indicated any adverse fetal or neonatal effects.

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Pharmacologist

cc:
NDA 18-654
NFM 120
NFM-120/JContrera init. 4/12/84
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mOR

NDA 18-654

120 601
ME 15

Date Completed: April 11, 1984
Date Assigned: January 19, 1984
Date of Submission: December 15, 1982
Date Received: December 15, 1982

MEDICAL OFFICER'S REVIEW

Name of Sponsor: Hoffman-LaRoche
Nutley, New Jersey 07110

Name of Drug: Generic: Midazolam Injectable

Category (Use) of Drug: Sedative for short diagnostic or endoscopic procedures.

Dosage Form and Route of Administration: Solution of midazolam hydrochloride 5 mg/ml in ampuls for parenteral injection.

Type of Submission: Original New Drug Application submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.1.

General Comments:

This review encompasses only a portion of the clinical submission comprised of 30 studies of midazolam as an intravenous sedative in patients undergoing diagnostic endoscopic or cardiovascular procedures. The endoscopic procedures included bronchoscopy, gastroscopy and cystoscopy. The cardiovascular procedures included cardiac catheterization, angiography and cardioversion. Studies were conducted with or without meperidine premedication and specific types of studies were conducted within a multicenter format and were pooled for analysis. The type of studies and their multicenter organization were as follows:

Table 1
STUDY ORGANIZATION

<u>Investigator</u>	<u>Study number</u>
<u>Protocol 2234A - Bronchoscopy Without Meperidine Premedication</u>	
Steinberg, H.	106
Robertson, J. K.	108
Ahmad, H.	112
Kvale, P.A.	121
<u>Protocol 2235A - Bronchoscopy With Meperidine Premedication</u>	
Khan, F. A.	107
Balchum, O. J.	117
Jenkinson, S. J.	118
Mariencheck, W. I.	123

Protocol 2236A - Cystoscopy Without Meperidine Premedication

Lawson, R. K.	105
Evans, A. T.	113
Wein, A. J.	119
Chasapakis, G.	150

Protocol 2237A - Cystoscopy With Meperidine Premedication (Females)

Witherington, R.	116
Witherington, R.	126

Protocol 2237B - Cystoscopy With Meperidine Premedication (Males)

Fair, W. R.	124
Corssen, G.	125
Hanno, P. N.	127
Lawson, R. K.	128

Protocol 2238A - Gastroscopy Without Meperidine Premedication

Lanza, F. I.	101
Dunn, D. G.	110
Isenberg, J. I.	120

Protocol 2239A - Gastroscopy With Meperidine Premedication

White, P. F.	102
Morrissey, J. F.	104

Protocol 2241A - Cardioversion Without Meperidine Premedication

Lee, T.	109

Protocol 2242A - Cardiac Catheterization With Meperidine Premedication

Gensini, G.	114
Hendrix, H.	115
Ludbrook, P. A.	122

Protocol 1032 - Cardiac Catheterization Without Meperidine Premedication (Hemodynamic Study)

Fragen, R.	007

Protocol 2243A - Angiography Without Meperidine Premedication

Ludbrook, P. A.	103
Ryan, T. J.	111

Pooled Study Summary

Study Nos. 106, 108, 112, 121, Protocol 2234A

Title: A comparison of Midazolam and Diazepam Administered Intravenously with Local Anesthesia for Bronchoscopy.

Subjects

Eighty three patients (ASA I-II) undergoing diagnostic bronchoscopy for the first time participated in the study. The study population consisted of 30 non-pregnant females and 53 males ranging in age from 20 to 85 years. In the midazolam group there were 28 males and 14 females with a mean age of 54.8 years (range 21-85). In the diazepam group there were 25 males and 16 females with a mean age of 55.9 years (range 20-85).

Results

Differences Among Study Centers

Efficacy data from the four patients in study #112 were not included in the efficacy analysis due to limited patient enrollment.

There was a major difference between study centers in the physicians' assessments of sedation. Several of the investigators experienced difficulties with the procedure since premedication with meperidine was not allowed. Dr. Shmad (Study #112) discontinued his study because of excessive coughing and gagging of his patients. Dr. Robertson (Study #108) experienced similar problems; however, these experiences were more pronounced in the midazolam group. Dr. Steinberg (Study 105) did not have these problems; however, he had to administer maintenance sedation doses of the test drugs to almost all of his patients (77%).

Deviations From Protocol

These are addressed in the individual study summaries.

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean initial doses of 0.110 mg/kg of midazolam and 0.166 mg/kg of diazepam. Forty two percent of the patients in the midazolam group and 48% of the diazepam group required maintenance sedation doses to complete the procedure. Most of these patients were from Dr. Steinberg's study. The mean total drug doses administered were 0.146 mg/kg of midazolam and 0.210 mg/kg of diazepam.

The meantime to reach the sedative end point was significantly shorter for the midazolam group (3 minutes vs. 5.8 minutes). The average duration of the bronchoscopies was similar between treatment groups.

Physician's Assessment

Diazepam patients were significantly more cooperative and had better muscle relaxation. One center (#108) contributed most to weighing the data against midazolam.

with Local Anesthesia for Bronchoscopy.

Patient's Assessment

Subject

One hour after the procedure, sedation was rated significantly better by the midazolam group; however, this difference did not remain significant by the following day. Most patients in both groups had little or no pain associated with the bronchoscopy and were willing to undergo a future procedure the same way.

young (range 21-50) in the diazepam group (mean 38) and 30 in the midazolam group (mean age of 55.7 years).

Trieger Test

There were increases in the number of dots missed and deviation from the dots in both treatment groups one hour after the bronchoscopy, with the midazolam patients displaying a statistically significant increase in deviation from the dots. By two hours these values demonstrated a downward trend, although they were still elevated.

Follow-Up Questionnaire for Amnesia

There was a small percentage of patients in each group with diminished recall of events prior to test drug administration. Following test administration both groups had diminished recall of scope introduction and withdrawal; however, midazolam patients had significantly less recall of the introduction of the bronchoscope. Significantly more patients in the midazolam group had diminished recall of the post-treatment Trieger Tests.

These are addressed in the individual study reports.

The results of the study are presented in the following tables. The midazolam group is listed first and the diazepam group second.

Safety

Table 1
Clinical Adverse Experiences

<u>Possibly and Probably Related Drug Effects</u>	<u>Midazolam</u>		<u>Diazepam</u>	
	<u># Pts.</u>	<u>Percent</u>	<u># Pts.</u>	<u>Percent</u>
<u>Respiratory System</u>				
Respiration Rate Increase	22	52.4	10	43.9
Respiration Rate Decrease	9	21.4	12	29.3
Respiratory Depression	1	2.4	0	0
Airway Obstruction	1	2.4	0	0
Coughing	1	2.4	0	0
Bronchospasm	1	2.4	0	0
<u>Cardiovascular System</u>				
Pulse Increase	12	23.6	13	31.7
Pulse Decrease	4	9.5	4	9.8
MAP Increase	1	2.4	4	9.8
MAP Decrease	9	21.4	4	9.8
Hypotension	1	2.4	0	0
Phlebitis	0	0	2	4.9
Tenderness of Vein	0	0	2	4.9
Redness of Vein	1	2.4	1	2.4
Induration of Vein	0	0	1	2.4
<u>Central Nervous</u>				
Headache	0	0	1	2.4
<u>Gastrointestinal</u>				
Vomiting	1	2.4	1	2.4
<u>Miscellaneous</u>				
Agitated	0	0	1	2.4
<u>Remotely Related Effects</u>				
Bradycardia	1	2.4	0	0
Blood loss	1	2.4	0	0

No changes in vital signs were observed during induction of sedation.

Summary and Conclusions

In this multicenter study the results of four randomized, double-blind parallel group studies included 83 patients undergoing diagnostic bronchoscopy for the first time, using atropine premedication and a topical anesthetic agent. Significantly less time was required by the midazolam-treated patients to reach the sedative and point. Forty two and forty eight percent of patients in the midazolam and diazepam groups respectively required maintenance sedation doses.

On the physician's assessment, significantly better muscle relaxation and cooperation were ascribed to the diazepam group. This protocol did not allow premedication with meperidine and several investigators experienced difficulty in performing the bronchoscopy because of excessive patient coughing and gagging.

On the one-hour patient questionnaire, midazolam-treated patients assessed quality of sedation as significantly better. There were no significant differences between group in willingness to undergo a future procedure the same way and for degree of pain associated with the bronchoscopy.

With respect to psychomotor recovery, midazolam patients has significantly more impairment one hour following the bronchoscopy.

Most patients could recall events prior to the test drug administration. Significantly more midazolam patients could not recall the bronchoscopy and the post treatment Triger Tests.

Most changes in vital signs were not clinically significant. One patient experienced hypotension and respiratory depression following the administration of midazolam. No corrective measures were required and the procedure was successfully completed. Another patient who received midazolam had too much muscle relaxation which caused brief occlusion of the airway by the tongue. One patient experienced severe agitation following the administration of diazepam forcing the investigator to cancel the procedure.

Two diazepam and one midazolam-treated patients had evidence of venous irritation at the intravenous injection site at the follow-up examination.

In this study midazolam was shown to be as safe and effective as diazepam in inducing sedation for bronchoscopy. The physicians did not rate midazolam as effective as diazepam for some parameters, but the patients experienced better sedation and had less recall of the procedure. Several physicians had difficulty in completing the bronchoscopy because of excessive coughing and gagging of the patients, and a relatively large percentage of patients required maintenance doses. These conditions may have occurred because of the elimination of a narcotic premedicant.

Study No. 106

Title: A Comparison of Midazolam and Diazepam Administered Intravenously With Local Anesthesia for Bronchoscopy

Investigator: The objective of this study was to compare the sedative and amnestic properties administered during local anesthesia for bronchoscopy.

Experimental Design

Randomized, double-blind study in 40 patients undergoing bronchoscopy for the first time. The design of this study was similar to that of study 121 since this was a multicenter study following the same protocol.

Subjects

There were 18 non-pregnant females and 22 males ranging in age from 25 to 85 years (ASA I-II). In the midazolam group there were 11 males and a females with a mean age of 58.8 years (range 25-82). In the diazepam group there were 11 males and 9 females with a mean age of 60.8 years (range 26-85).

Study Drugs: See Study 121.

ResultsDeviations from Protocol

Patient (diazepam, 0.429 mg/kg) was excluded from efficacy analyses for receiving an excludable concomitant medication (Percodan) within twenty four hours of the procedure.

Three patients omitted answering a question on the 24 hour questionnaire:

Patient	(Midazolam) - rual injection in thigh
Patient	(Diazepam) - Future procedure done same way
Patient	(Diazepam) - Recall scope introduction

Most patients did not have vital sign measurements taken after the bronchoscopy; therefore, only a few patients' data were analyzed for changes in vital signs during the recovery period.

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.094 mg/kg of midazolam and 0.131 mg/kg of diazepam. Seventy percent of the midazolam group and 84 percent of the diazepam group required maintenance sedation doses to complete the procedure. Midazolam-treated patients required a mean total drug dose of 0.158 mg/kg, while diazepam-treated patients required 0.236 mg/kg. There was no significant difference between groups with respect to time to reach the sedative endpoint.

Physician's Assessment

The physician's assessment of sedation was in most instances "good" to "excellent" for both midazolam and diazepam treatment groups. There were no significant differences between treatments in the physician's assessment of sedation.

Patient's Assessment

Midazolam patients rated quality of sedation significantly better one hour after bronchoscopy; however, there was no significant difference between treatments in the following day. Midazolam - treated patients reported significantly less pain associated with the bronchoscopy. Most patients were willing to undergo the procedure the same way again.

Trieger Test

Midazolam-treated patients missed significantly more dots one hour after the procedure, toward the baseline values.

Follow-Up Questionnaire for Amnesia

One hour after the procedure, both treatment groups had diminished recall of the bronchoscopy; however, midazolam - treated patients had significantly less recall of the procedure. Diminished recall was extended to two hours in several patients in both treatment groups with respect to failure to recall the post-treatment Trieger Tests.

Safety

Patient (diazepam) had evidence of phlebitis (erythema and induration) for three days following the study. Tenderness of the intravenous injection site was also present for nine days following the study. This patient also had a headache following the procedure. Patient (midazolam) experienced bradycardia; however, this was considered to be remotely related to the test drug treatment.

Patient (Midazolam) - recall of procedure
Patient (Diazepam) - recall of procedure
Patient (Diazepam) - recall of procedure

Comparable levels of sedation were attained with a dose of 0.05mg/kg in
and 44 percent of the diazepam group received an intravenous injection of
sedation was maintained for 15 minutes after the procedure. The
level of sedation was significantly higher in the midazolam group
than in the diazepam group at one hour after the procedure.

Table 1Clinical Adverse Experiences

<u>Possibly and Probably Related Drug Expects</u>	<u>Number of Patients</u>	
	<u>Midazolam</u>	<u>Diazepam</u>
<u>Respiratory System</u>		
Respiration Rate Increase	5	5
Respiration Rate Decrease	2	1
<u>Cardiovascular System</u>		
Pulse-Increase	1	2
Pulse-Decrease	1	0
MAP - Increase	0	2
MAP - Decrease	0	1
Phlebitis	0	1
Tenderness of Vein	0	1
<u>Central Nervous</u>		
Headache	0	1
<u>Remotely Related Drug Effect</u>		
<u>Cardiovascular</u>		
Bradycardia	1	0

Most changes in vital signs were transient and were most often associated with the bronchoscopy. No changes in vital signs were observed during induction of sedation.

Summary and Conclusions

This randomized, double-blind study compared the use of midazolam with diazepam to provide sedation during bronchoscopy. As adjuncts to local anesthetic agents, both drugs were effective intravenous sedative agents for bronchoscopy. Ratings of sedation by the physician were in most instances "good" to "excellent" for both test medications. One hour after the bronchoscopy, midazolam patients evaluated quality of sedation significantly better and reported significantly less pain associated with the procedure than did diazepam-treated patients.

One hour after the procedure, both treatment groups had diminished recall of the bronchoscopy; however, the midazolam group had significantly less recall of the procedure. Midazolam-treated patients had significantly less recall of the introduction of the bronchoscopy, although most patients had diminished recall of the introduction and withdrawal of the bronchoscope. Several patients in both treatment groups had diminished recall for the post-treatment

Trieger Tests extending to two hours. Midazolam patients missed significantly more tests on the one hour Trieger Test, but at two hours the results had returned to near the baseline value.

Transient fluctuations in vital signs were observed in both treatment groups but were not considered clinically significant. One diazepam-treated patient had evidence of phlebitis. One midazolam-treated patient had bradycardia, but this was considered to be remotely related to the test drug.

This study showed that midazolam, when used in combination with a local anesthetic agent, is as safe and effective as diazepam in inducing sedation for bronchoscopy. It was also effective in inducing diminished recall of the procedure.

Summary and Conclusions

Midazolam provided sedation during bronchoscopy. Ratings of sedation were "good" to "excellent" for both test procedures. Midazolam was considered to be a safe and effective sedative for bronchoscopy and permitted significantly less recall of the procedure.

patients in both treatment groups had diminished recall of the procedure.

Study No. 108

Title: A Comparison of Midazolam and Diazepam Administered Intravenously with Local Anesthesia for Bronchoscopy.

Investigator: K. Joy Robertson, M.D.

Objective: The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam when administered during local anesthesia for bronchoscopy.

Experimental Design

Randomized, double-blind study in the patients undergoing bronchoscopy for the first time. The design of this study was similar to that of Study 121 since this was a multicenter study following the same protocol.

Subjects

There were 3 non-pregnant females and 13 males ranging in age from 20 to 80 years (ASA I-II). In the midazolam group there were 7 males and 1 female with a mean age of 36.5 years (range 21-69). In the diazepam group there were 6 males and 2 females with a mean age of 41.3 years (range 20-80).

Study Drugs: See Study 121

ResultsDeviations from Protocol

Patient: who received 0.250 mg/kg of diazepam, developed severe agitation which required termination of the bronchoscopy. This patient's data were excluded from all efficacy tables.

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.119 mg/kg of midazolam and 0.224 mg/kg of diazepam. One midazolam and two diazepam patients required additional doses to maintain sedation. Midazolam-treated patients required a shorter mean time to sedation of 2.45 minutes compared with 4.75 minutes for diazepam-treated patients.

Physician's Assessment

There were no significant differences between treatment groups. Control of laryngospasm "excellent" in both treatment groups.

Patient's Assessment of Sedation

On both rating occasions, most patients in both treatment groups reported the quality of sedation as "good" or "excellent". All patients described little or no pain associated with the bronchoscopy. Most patients said that they would elect to undergo the procedure the same way again.

Trieger Test

Patients in both treatment groups had an increase in number of dots missed and total deviation from the dots compared with baseline values at one hour following the bronchoscopy. At two hours these values were returning toward baseline for midazolam patients while diazepam patients had an increase in these values compared with their one hour results.

Follow-Up Questionnaire for Amnesia

Several patients in each group had no recall of spraying of the throat. Failure of recall of bronchoscope introduction and withdrawal was experienced by most patients in both treatment groups. Several patients had prolonged failure of recall since on the following day they could not recall the post-treatment Trieger Tests.

Safety

One patient developed severe agitation after receiving 0.250 mg/kg of diazepam which caused the investigator to cancel the bronchoscopy. One midazolam-treated patient developed vomiting and coughing.

Table 1Clinical Adverse Experiences

<u>Possibly and Probably Related Drug Effects</u>	<u>Number of patients</u>	
	<u>Midazolam</u>	<u>Diazepam</u>
<u>Respiratory System</u>		
Respiratory Rate Increase	7	5
Respiratory Rate Decrease	2	4
Coughing	1	0
<u>Cardiovascular System</u>		
Pulse Increase	6	4
Pulse Decrease	1	0
MAP Increase	1	1
VAP Decrease	2	1
<u>Gastrointestinal</u>		
Vomiting	1	0
<u>Miscellaneous</u>		
Agitated	0	1

No changes in vital signs were observed during induction of intravenous sedation. Most changes were transient and were most often associated with the bronchoscopy. A severe increase in mean arterial pressure was observed in one midazolam patient both during bronchoscopy and recovery. Severe increases in pulse rate and respiration rate both during bronchoscopy and recovery were observed in several patients in both treatment groups. One diazepam patient also had a severe decrease in respiration rate during recovery.

Summary and Conclusions

This study was still in progress at the time of submission and a statistical analysis of the results was not undertaken due to the limited number of patients studied.

One patient developed severe agitation after receiving diazepam, which forced the investigator to cancel the bronchoscopy. One midazolam - treated patient experienced vomiting and coughing. Transient fluctuations in blood pressure, pulse and respiration rate were noted but were not considered clinically significant. No patient in either treatment group had evidence of venous irritation following the study.

Study No. 112

Title: A Comparison of Midazolam and Diazepam Administered Intravenously with Local Anesthesia for Bronchoscopy.

Investigator: Huzaffar Shmad, M.D.

Objective: The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam when administered during local anesthesia for bronchoscopy.

Experimental Design

Randomized, double-blind study in 4 patients undergoing bronchoscopy for the first time. The design of this study was similar to that of Study 121 since this was a multicenter study following the same protocol.

Subjects

There were four males ranging in age from 53 to 60 years (ASA I-II). In the midazolam group there were 3 patients, 53 to 55 years of age in the diazepam group there was one patient, 60 years of age.

Study Drugs: See Study 121.

Results

This study was prematurely discontinued after entry of 4 patients due to difficulty encountered by the investigator in performing the bronchoscopy without using a narcotic cough suppressant (investigator's routine procedure) as a premedication. The investigator rated both drugs poor in controlling the cough reflex.

Safety

A 54 year old patient with a history of arteriosclerotic heart disease, experienced hypotension and respiratory depression following administration of 0.181 mg/kg of midazolam. No corrective measures were required, and the bronchoscopy was successfully completed. This patient also experienced coughing during the procedure. For three days following the study, redness of the vein was also observed.

Patient 1 (midazolam) experienced too much muscle relaxation which caused brief occlusion of the airway by the tongue. This patient also experienced coughing during the bronchoscopy.

Table 1Clinical Adverse Experiences

<u>Possibly and Probably Related Drug Effects</u>	<u>Number of Patients</u>	
	<u>Midazolam</u>	<u>Diazepam</u>
<u>Respiratory System</u>		
Respiration Rate Increase	3	1
Respiration Rate Decrease	3	1
Respiratory Depression	1	0
Airway obstruction	1	0
<u>Cardiovascular system</u>		
Pulse Increase	2	1
Pulse Decrease	0	1
MAP Decrease	2	1
Hypotension	1	0
Redness of Vein	1	0

No changes in vital signs were observed during the induction of sedation. Midazolam-treated patients had severe increases or decreases in respiration rate. One midazolam patient also had a severe increase in pulse rate.

Summary

A statistical analysis of this study was not possible due to the limited number of patients studied. Changes in vital signs were observed in all patients both during the bronchoscopy and recovery. One midazolam-treated patient experienced respiratory depression and hypotension during the procedure, however, no corrective treatment was necessary. Another patient who received midazolam had excessive muscle relaxation of the tongue which caused brief occlusion of the airway. These two patients also experienced coughing during the procedure. One midazolam-treated patient experienced redness at the intravenous injection site for three days following the procedure.

Study No. 121

Title: A comparison of Midazolam and Diazepam Administered Intravenously with Local Anesthesia for Bronchoscopy.

Investigator: Paul A. Kvale, M.D.

Objective: The objective of this study was to compare sedative and amnestic properties of intravenous midazolam and diazepam when administered during local anesthesia for bronchoscopy.

Experimental Design

This study was in progress at the time of submission; therefore, this report contains an analysis of the results in the first 23 patients. This is a randomized, double-blind, parallel-group study.

Prior to bronchoscopy midazolam or diazepam was administered by random coded assignment. Immediately following the bronchoscopy the physician, who was unaware as to which test medication had been administered evaluated as excellent, good, fair or poor the sedative effects produced by the test medication. These assessments included: (1) patient cooperation, (2) muscle relaxation, (3) ease of bronchoscopic examination, (4) control of gag reflex, (5) control of laryngospasm, (6) control of bronchospasm, (7) control of cough reflex, (8) control of retching and vomiting, (9) control of salivation, and (10) overall tolerance of the procedure. One hour after bronchoscopy and one day later in a follow-up questionnaire, patients evaluated the sedation during the procedure as excellent, good, fair or poor. Additionally, on both occasions, patients were asked whether they would elect to undergo a future bronchoscopy the same way, if necessary. One hour after bronchoscopy patients evaluated the bronchoscopic procedure as not painful, somewhat painful or very painful and whether they could recall none, some or all of the bronchoscopy. In the follow-up questionnaire, patients were also asked whether they could recall clearly, vaguely or not at all events before, during and after bronchoscopy.

Recovery from sedation was assessed by the Trieger Test which was completed by the patient before medication (baseline) and at 60 and 120 minutes following the completion of the bronchoscopy. Each Trieger Test was evaluated for the number of dots missed and the total deviation (mm) from the dots.

Blood pressure, respiratory rate and pulse rate were monitored before, during and after bronchoscopy. Changes in vital signs greater than 20% from baseline were identified as possible adverse experiences. The severity of these changes were categorized as:

- mild - a change $\geq$ 20 percent but $<$ 30 percent from baseline
- moderate - a change $\geq$ 30 percent but $<$ 50 percent from baseline
- severe - a change $\geq$ 50 percent from baseline or treatment required.

Clinical adverse experiences were further categorized according to the phase of the study. The phases of the study were defined as follows:

induction = period of test drug administration
 maintenance = period of bronchoscopy
 recovery = post bronchoscopy until discharge

Seven to 14 days following the procedure the intravenous injection site was examined for tenderness, redness and induration.

Subjects

There were 9 non-pregnant females and 14 males ranging in age from 23-85 years. In the midazolam group there were 7 males and 4 females with a mean age of 61.2 years (range 34-85). In the diazepam group there were 7 males and 5 females with a mean age of 57.1 years (range 23-84).

Study Drugs

Thirty minutes before bronchoscopy atropine 0.5 - 0.6 mg was administered intramuscularly. Following topical anesthetic administration, 10-15 mg of either midazolam or diazepam was administered intravenously over a 2-3 minute period. Elderly patients (as identified by the investigator) received 5.0-7.5 mg of the test medications over the same time interval. Incremental doses (25% of initial dose) were administered, if necessary, until the patient's speech became thickened and slurred but the patient was still responsive to verbal commands. When needed, additional doses were administered to maintain sedation.

Results

Deviation from Protocol

Midazolam patient (0.078 mg/kg) was terminated from the study due to pharyngeal bleeding and bronchospasm resulting from a pre-existing condition. Diazepam patient did not receive the total injected dose (3 ml) intravenously since the IV infiltrated during injection. They were excluded from efficacy analysis but their data was included in all safety analyses.

The Trieger Test results of midazolam patient were not included in the efficacy analysis since the patient was uncooperative in completing the Trieger Tests. This patient did not complete the 24 hour questionnaire. The responses to recall of the Trieger Test by midazolam patient were not included in the analysis because the patient recalled only one test but did not know which one it was.

Three patients did not answer several questions on the one or 24 hour questionnaires:

Patient (midazolam) - One hour questionnaire:
Future procedure same way

Patient (diazepam) - 24 hour questionnaire: 40
Future procedure same way

Patient (midazolam) - 24 hour questionnaire:
Recall of scope withdrawal

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.118 mg/kg of midazolam and 0.144 mg/kg of diazepam. Patient required an additional 10.038 mg/kg of midazolam to maintain sedation. The average time to reach the sedative end point was significantly shorter for midazolam than for diazepam, the former time being less than half that of the latter drug. The duration of bronchoscopy was similar for both groups.

Physician's Assessment

Assessments of sedation were in most instances "good" to "excellent" for both groups. Control of cough reflex was rated "fair" to "good" in both groups. There were no significant intergroup differences.

Patient's Assessment

One hour after the procedure, quality of sedation was rated significantly better by midazolam-treated patients, although on the following day this difference was not present. Most patients reported little or no pain associated with the bronchoscopy and indicated they would elect to undergo a future procedure the same way again.

Trieger Test

There were no statistically significant differences between the two groups in recovery from sedation. There was an increase in number of dots missed and total deviation from the dots compared with the baseline in both groups one hour after bronchoscopy. By two hours the results returned toward baseline values.

Follow-Up Questionnaire for Amnesia

There were no significant differences between treatment groups on any of the recall questions. All but one midazolam patient could recall introduction and withdrawal of the bronchoscope, while more than half of the diazepam patients could recall either the introduction or withdrawal of the bronchoscope. Failure to recall the post-treatment Trieger Tests was more pronounced for the one hour test (4/9) than for the two hour test (6/9).

Safety

Patient [redacted] (midazolam) had pharyngeal bleeding during the procedure which aggravated a pre-existing cough and caused the patient to have bronchospasm. The bleeding was controlled by intubation and Adrenalin. Bronchospasm was controlled with Demerol, Adrenalin, Xylocaine, Medrol and Vaponefrin.

Patient [redacted] (diazepam) developed phlebitis at the intravenous injection site. Tenderness, redness and induration were observed for 10 days following the study.

Table 1Clinical Adverse Experiences

<u>Possibly and Probably Related Drug Effects</u>	<u>No. Pts.</u>	
	<u>Midazolam</u>	<u>Diazepam</u>
<u>Respiratory System</u>		
Respiration Rate Increase	7	6
Respiration Rate Decrease	2	6
Bronchospasm	1	0
<u>Cardiovascular System</u>		
Pulse Increase	3	6
Pulse Decrease	2	3
MAP Increase	0	1
MAP Decrease	5	1
Tenderness of Vein	0	1
Redness of Vein	0	1
Induration of Vein	0	1
<u>Integumentary</u>		
Phlebitis at Site of Injection	0	1
<u>Remotely Related Drug Effect</u>		
<u>emic-Lymphatic</u>	1	0

No changes in vital signs were observed during induction of intravenous sedation. Most changes in vital signs were transient and were most often associated with the bronchoscopy. Most changes were mild or moderate with very few classified as severe. Severe increases in respiration rate were observed in both treatment groups during both the bronchoscopy and during the recovery period. One diazepam - treated patient had a severe decrease in respiration rate during the recovery period.

Summary and Conclusions

This randomized, double-blind study compared the use of midazolam with diazepam to provide sedation during bronchoscopy. The study was still in progress at the time of submission and this report represents the results in 23 patients. As adjuncts to local anesthetic agents, both drugs were effective intravenous sedative agents for bronchoscopy. Ratings of sedation by the physician were "good" to "excellent" for both test medications except for control of cough reflex which was rated "fair" to good. Quality of sedation was rated significantly better by the midazolam patients one hour later; however, this difference was not present on the following day. Most patients in both treatment groups reported little or no pain associated with the bronchoscopy and indicated that they would elect to undergo the procedure the same way again.

Recovery from sedation was comparable between treatments. Both groups showed some impairment of performance one hour following bronchoscopy. Failure to recall the bronchoscopy was induced in all but one midazolam patient, but more than half of the diazepam patients had recall of the procedure. Failure of recall was extended in some midazolam patients for two hours.

One midazolam - treated patient developed pharyngeal bleeding during the procedure which aggravated a pre-existing cough and caused the patient to have bronchospasm. This was treated and relieved. One diazepam - treated patient had evidence of phlebitis at the intravenous injection site for 10 days following the study. Transient fluctuations in vital signs were noted in both treatment groups but were not considered clinically significant.

This study showed that midazolam, in combination with local anesthetic, was safely used to induce sedation during bronchoscopy. Midazolam was as effective as diazepam in providing patient sedation, and was superior in inducing failure of recall for the procedure.

Pooled Study Summary

Study Nos. 107, 117, 118, 123, Protocol 2235A

Title: A Comparison of Midazolam and Diazepam In Combination With
Heperidine During Local Anesthesia for Bronchoscopy

Subjects

Eighty eight patients (ASA I, or II) undergoing diagnostic bronchoscopy for the first time participated in the study. The study population consisted of 36 non-pregnant females and 52 males ranging in age from 20 to 79 years. In the midazolam group there were 43 patients comprised of 22 males and 21 females with a mean age of 49.8 years (range 25-72). In the diazepam group there were 45 patients comprised of 30 males and 15 females with a mean age of 53/2 years (range 20-79).

Results

Differences Between Study Centers

An additional dose of test medication to maintain sedation was administered to six midazolam and five diazepam patients in Dr. Balchum's study (#117). None of the patients in the other studies required maintenance sedation doses. The need for maintenance sedation doses in this study was related to the longer time required for completion of the bronchoscopy. In the other three studies, the average length of the procedure was 25 minutes compared with 51 minutes in Dr. Balchum's study.

Deviations from Protocol

These are addressed in the individual study reports.

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean initial doses of 0.094 mg/kg of midazolam and 0.104 mg/kg of diazepam. An additional dose to maintain sedation was required by six (6 of 9) midazolam and five (5 of 10) diazepam patients in Dr. Balchum's study (#117). The reason for this has already been detailed in the beginning of this section. The mean time to reach the sedative end point of slurred speech was 4.4 minutes for both groups of patients.

Physician's Assessment of Sedation

A 4-point scale (excellent, good, fair, poor) was used by the physician to assess the sedative effects of the test medications. There were no significant differences between treatment groups in the assessment. Most parameters were assessed as "good" or "excellent" by the physician. Control of cough reflex, however, was only rated "fair" to "good" for both test drugs.

Patient's Assessment of Sedation

On two occasions, one hour after the procedure and on the following day, patients assessed the sedative effects of the test drugs. One hour after the procedure, there was no significant difference between treatment groups. On the following day, however, midazolam-treated patients rated sedation significantly better. The majority of midazolam patients (97%) and all of the diazepam patients reported little or no pain associated with the procedure. Most patients were willing to have a future bronchoscopy done the same way.

Trieger Test

There were no statistically significant differences between treatment groups in psychomotor recovery from sedation. There were increases in number of dots missed and deviation from the dots in both treatment groups one hour after bronchoscopy. At two hours the results in both treatment groups had returned to near the baseline values. While the midazolam group approached closer to the baseline values, the difference was not statistically significant.

Follow-Up Questionnaire for Amnesia

Most patients in both groups could recall events performed before test drug administration. A statistically significantly greater number of midazolam patients had diminished recall of the baseline Trieger Test. Following test drug administration, both test groups had diminished recall of the bronchoscopy. Midazolam-treated patients had significantly less recall of scope introduction. The majority of patients recalled the one and two hour Trieger Tests.

Safety

Three patients who received midazolam experienced adverse reactions which forced cancellation of the bronchoscopy. These adverse experiences were all felt to be related to the combined effects of midazolam/meperidine.

<u>Study</u>	<u>Patient number</u>	<u>Adverse Reactions</u>
117		hypotension and apnea
107		deep sedation and apnea
107		deep sedation and hypotension

00000

Table 1
Clinical Adverse Experiences

	<u>Midazolam</u>		<u>Diazepam</u>	
	<u># pts.</u>	<u>Percent</u>	<u># pts.</u>	<u>Percent</u>
<u>Possibly and Probably Related Drug Effects</u>				
<u>Respiratory System</u>				
Respiration Rate Increase	23	53.5	29	64.4
Respiration Rate Decrease	13	30.2	16	35.6
Apnea	2	4.7	1	2.2
<u>Cardiovascular System</u>				
Pulse Increase	18	41.9	21	46.7
Pulse Decrease	10	23.3	6	13.3
MAP Increase	6	14.0	10	22.2
MAP Decrease	11	25.6	5	11.1
Hypotension	2	4.7	1	2.2
Tenderness of Vein	0	0	1	2.2
Redness of Vein	0	0	1	2.2
Induration of Vein	1	2.3	0	0
<u>Central Nervous</u>				
Headache	1	2.3	0	0
<u>Gastrointestinal</u>				
Nausea	2	4.7	2	4.4
Vomiting	0	0	1	2.2
<u>Musculoskeletal</u>				
Hiccoughs	1	2.3	0	0
<u>Integumentary</u>				
Pain During Injection of study drug	0	0	4	8.9
<u>Miscellaneous</u>				
Chest Pain	0	0	1	2.2
Deep Sedation	2	4.7	0	0
<u>Remotely Related Drug Effect</u>				
Laryngitis	1	2.3	0	0
Epiglottitis	1	2.3	0	0
Laryngospasms	0	0	1	2.2
Headache	1	2.3	0	0
Clenching of Jaws	1	2.3	0	0
Blurring of Vision	1	2.3	0	0
Number of Adverse Experiences Reported	97		100	
Number of Patients with Adverse Experiences	38	88.4	41	91.1
Number of Patients Treated	43		45	

Summary and Conclusions

In this multicenter study the results from randomized, double-blind parallel group studies included 88 adults. It was demonstrated that both midazolam and diazepam were effective intravenous sedative agents for bronchoscopy when used as adjuncts to intramuscular meperidine and local anesthetic. All patients received meperidine, atropine, and a topical anesthetic agent prior to the procedure. Comparable levels of sedation (slurred speech) were attained with mean doses of 0.094 mg/kg of midazolam and 0.104 mg/kg of diazepam in a mean time of 4.4 minutes with either drug.

The physician's evaluation of the sedative properties of the test drugs were similar for both drugs. Patients' assessments were not significantly different one hour after the procedure; however, on the following day midazolam-treated patients rated sedation as significantly better. Most patients in both test groups reported little or no pain associated with the bronchoscopy and were willing to undergo a future procedure the same way.

Midazolam produced significantly greater anterograde recall impairment. One hour after the procedure, only 11% (4 of 35) of midazolam-treated patients could recall the procedure compared with 45% (19 of 42) of diazepam-treated patients.

Psychomotor recovery from sedation as assessed by the Trieger Test was comparable between treatments. Both treatment groups had impairment of psychomotor performance one hour after the procedure; however, two hours post-treatment the results in both treatment groups approached baseline values, demonstrating recovery from sedation.

There were reports of hypotension, apnea and deep sedation in both groups; however, in the midazolam-treated group three patients with these reactions had their bronchoscopies cancelled. No cancellations for these reasons occurred in the diazepam-treated group. There were reports of laryngospasm (diazepam) and epiglottitis and laryngitis (midazolam) which forced cancellation of the procedure. These events were all related to underlying patient conditions. These reactions were attributed to the combined effects of meperidine and the benzodiazepine. One patient in each test group had evidence of venous irritation at the follow-up examination.

This study demonstrated that IV midazolam, when used in combination with meperidine, atropine and a topical anesthetic agent is as safe and effective as diazepam in inducing sedation for bronchoscopy. Midazolam impaired recall of the procedure more effectively. There were several instances of adverse experiences in both treatment groups (deep sedation, hypotension or apnea). These effects occurred more frequently and were more severe in the midazolam group. These adverse effects were attributed to the combined effects of meperidine and midazolam.

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Study No. 107

Title: A Comparison of Midazolam and Diazepam in Combination With Meperidine During Local Anesthesia for Bronchoscopy

Investigator: Faroque A. Khan, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in adults undergoing bronchoscopy for the first time.

Experimental Design

Randomized, double-blind study in 22 adults undergoing bronchoscopy. The design of this study was similar to that of study 117 since this was a multicenter study following the same protocol.

Subjects

There were 8 non-pregnant females and 14 males ranging in age from 34 to 78 years. In the midazolam group there were 7 males and 5 females with a mean age of 53.3 years (range 36-63). In the diazepam group there were 7 males and 3 females with a mean age of 60.6 years (range 34-78).

Study Drugs: See Study 117.

Results

Deviations from Protocol

Four midazolam | and one diazepam patient | were excluded from all efficacy analyses.

Patients | and | were excluded due to violations of the protocol. Patient | did not complete the Trieger Test. For patient | the physician's assessment and patient questionnaires were not returned. Patient | and | experienced adverse effects (deep sedation with hypotension or coma) which required the postponement of bronchoscopy to a later date. Patient | experienced discomfort resulting from severe epiglottitis and laryngitis forcing the cancellation of the bronchoscopy. All patients who received test medications were included in safety analyses.

Only the baseline and one-hour Trieger Test Results were analyzed for patient | of the midazolam group. One of the Trieger Tests, done 10 minutes after the procedure, was discounted.

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.060 mg/kg of midazolam and 0.075 mg/kg of diazepam. The mean time to reach the sedative end point (slurred speech) was similar in both groups (midazolam: 7.77 minutes, diazepam: 6.94 minutes) for similar mean durations of bronchoscopy.

Physician's Assessment of Sedation

The physician's assessment of sedation was in most instances "fair" to "good" for both midazolam and diazepam-treated patients. There were no statistically significant differences between treatments in the physician's assessment of sedation.

Patient's Assessment of Sedation

One hour after the procedure 5/8 midazolam-treated patients rated the sedation "good" to "excellent" compared with 9/9 diazepam patients.

On the following day, 7/8 midazolam patients rated their sedation "good" to "excellent" compared with 9/9 diazepam patients, however, 5 of the former patients rated their treatment excellent compared with 2 diazepam patients. All patients reported little or no pain associated with the bronchoscopy and the majority of patients in both groups indicated that they would undergo future bronchoscopy the same way.

Trieger Test

On the one-hour Trieger Test, midazolam-treated patients had a greater number of dots missed and total deviation from the dots compared with baseline values than diazepam-treated patients, however, the differences were not statistically significant. By two hours, both treatment groups had returned toward the baseline values.

Follow-Up Questionnaire for Amnesia

There were no significant differences between treatments on any of the recall questions. Most midazolam and diazepam-treated patients could recall events prior to the test drug administration including the baseline Trieger Test, the meperidine injection and throat spraying, indicating absence of retrograde failure of recall. One hour after the procedure more midazolam than diazepam patients could not recall the bronchoscopy. Anterograde failure of recall, defined as lack of recall of events following the administration of the test drug, was observed in about half of the patients in both treatment groups. This extended for 5 of 8 midazolam patients and 8 of 8 diazepam patients to two hours with respect to failure to recall the post-treatment Trieger Tests.

Safety

Two patients who received midazolam had deep sedation requiring cancellation of the bronchoscopy. Patient , a 60-year old female with a history of atrial fibrillation and grand mal seizures, experienced deep sedation and hypotension after receiving 0.909 mg/kg of meperidine and 0.091 mg/kg of midazolam. Dopamine (60 mg) was given to reverse the hypotension. A 50 year old male patient experienced deep sedation and apnea (for 1 to 2 minutes) after receiving 0.833 mg/kg of meperidine and 0.083 mg/kg of midazolam. Narcan (0.4 mg) was administered and breathing resumed spontaneously. One diazepam-treated patient experienced mild hypotension upon completion of induction. No corrective measures were required; consequently, the bronchoscopy was successfully completed.

One midazolam patient had induration of the vein extending 2 cm proximal to the injection site for five days following the procedure. This patient also had mild blurring of vision and headache following the procedure; however, these symptoms were considered to be only remotely related to midazolam treatment by the investigator.

Changes in Vital Signs

The following tables indicate in which phase of the study the changes in vital signs occurred and the severity of the changes. Most changes were mild to moderate and were most often associated with the bronchoscopy. Patient who received diazepam, had a severe decrease in pulse rate during recovery. Three midazolam-treated patients had severe increases in respiration rates, one during bronchoscopy and two during recovery.

Table 1

Changes From Baseline For Mean Arterial Pressure

	Number of Patients	
	Midazolam	Diazepam
<u>Number of Patients Studied</u>	12	10
<u>During Induction of IV Sedation</u>		
Decrease (20-30%)	1	2
<u>During Bronchoscopy</u>		
Decrease (20-30%)	1	-
Decrease (30-50%)	1	-
Increase (20-30%)	1	-
<u>During Recovery</u>		
Decrease (20-30%)	4	-
Decrease (30-50%)	1	1

0.0008

Table 2

Changes From Baseline For Pulse Rate

	Number of Patients	
	Midazolam	Diazepam
<u>Number of Patients Studied</u>	12	10
<u>During Induction of IV Sedation</u>		
Decrease (20-30%)	1	-
Increase (30-50%)	-	1
<u>During Bronchoscopy</u>		
Decrease (20-30%)	1	-
Increase (20-30%)	1	3
Increase (30-50%)	2	1
<u>During Recovery</u>		
Decrease (20-30%)	1	1
Decrease (30-50%)	-	1
Decrease ($\geq$ 50%)	-	1
Increase (20-30%)	1	-
Increase (30-50%)	2	1

Table 3

Changes From Baseline For Respiration Rate

	Number of Patients	
	Midazolam	Diazepam
<u>Number of Patients Studied</u>	12	10 ^a
<u>During Induction of IV Sedation</u>		
Decrease (20-30%)	-	1
Increase (20-30%)	-	1
<u>During Bronchoscopy</u>		
Decrease (20-30%)	-	3
Increase (20-30%)	-	2
Increase (30-50%)	-	3
Increase ($\geq$ 50%)	1	-
<u>During Recovery</u>		
Decrease (20-30%)	2	2
Decrease (30-50%)	2	-
Increase (20-30%)	1	4
Increase (30-50%)	3	-
Increase ($\geq$ 50%)	2	-

Summary and Conclusions

This randomized, double-blind study included 22 patients, and demonstrated that both midazolam and diazepam were effective intravenous sedative agents for bronchoscopy, when used as adjuncts to intramuscular meperidine and local anesthetic. Favorable assessments of sedation were given in most instances by the physician. Favorable ratings for sedation were given for both test medications by the patients with most indicating that they would elect to undergo the procedure the same way again. All patients reported little or no pain associated with the bronchoscopy.

There were no statistically significant differences between the treatments on the Trieger Test; however, one hour following the bronchoscopy the midazolam group had a greater impairment of psychomotor performance represented by both missed dots and deviation from the dots. With respect to amnesia; one hour after the bronchoscopy more midazolam than diazepam-treated patients would not recall the procedure. Most patients in both groups had lack of retrograde amnesia by the following day, while about half the patients had diminished recall of the procedure on the following day.

Induration was noted at the intravenous injection site of one midazolam patient. Two patients who received midazolam experienced deep sedation with hypotension or apnea which required treatment. One diazepam-treated patient had hypotension, but no treatment was necessary.

Midazolam was shown in this study to be a useful sedative agent when used in combination with meperidine and a topical anesthetic agent. It was comparable to diazepam with respect to effectiveness. Depression leading to apnea or hypotension occurred in several cases with these agents.

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Study No. 117

Title: A Comparison of Midazolam and Diazepam In Combination With Neperidine During Local Anesthesia for Bronchoscopy

Investigator: Oscar Balchum, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in adults undergoing bronchoscopy for the first time.

Experimental Design

Randomized, double-blind study in 21 adults undergoing bronchoscopy.

Prior to bronchoscopy midazolam or diazepam was administered by random coded assignment. Immediately following bronchoscopy, the physician, who was unaware as to which test medication had been administered, evaluated as excellent, good, fair or poor the sedative effects produced by the test medication. These assessments included: (1) patient cooperation, (2) muscle relaxation, (3) ease of bronchoscopic examination, (4) control of gag reflex, (5) control of laryngospasm, (6) control of bronchospasm, (7) control of cough reflex, (8) control of retching and vomiting, (9) control of salivation and (10) overall tolerance of the procedure. One hour after bronchoscopy and one day later in a follow-up questionnaire, patients evaluated the sedation during the procedure as excellent, good, fair or poor. Additionally, on both occasions, patients were asked whether they would elect to undergo a future bronchoscopy the same way, if necessary. One hour after bronchoscopy, patients evaluated the procedure as not painful, somewhat painful or very painful and whether they could recall none, some or all of the bronchoscopy. In the follow-up questionnaire, patients were also asked whether they could recall clearly, vaguely or not at all events before, during and after bronchoscopy.

Recovery from sedation was assessed by the Trieger Test which was completed by the patient before medication (baseline) and at 60 and 120 minutes following the completion of the bronchoscopy. Each Trieger Test was evaluated for the number of dots missed and the total deviation (mm) from the dots.

Blood pressure, respiratory rate and pulse rate were monitored before, during and after bronchoscopy. Changes in vital signs greater than 20% from baseline were identified as possible adverse experiences. The severity of these changes were categorized as:

mild = a change $\geq$ 20 percent but $<$ 30 percent from baseline
moderate = a change $\geq$ 30 percent by $<$ 50 percent from baseline
severe = a change $\geq$ 50 percent from baseline or treatment required.

000031

Clinical adverse experiences were further categorized according to the phase of the study. The phases of the study were defined as follows:

induction = period of test drug administration

maintenance = period of bronchoscopy

recovery = post-bronchoscopy until discharge

Seven to 14 days following the study, the intravenous injection site was examined for redness, tenderness and induration.

Subjects

There were 7 non-pregnant females and 14 males, ranging in age from 26 to 77 years. In the midazolam group there were 6 males and 4 females with a mean age of 44.0 years (range 26-72). In the diazepam group there were 8 males and 3 females with a mean age of 51.2 years (range 34-77).

Study Drugs

Thirty minutes before bronchoscopy, meperidine 50 mg and atropine 0.5 mg were administered intramuscularly to the patients. Following topical anesthetic administration, 5.0-7.5 mg of either midazolam or diazepam were administered intravenously over a 2-3 minute period. Elderly patients (as identified by the investigator) received 2.5-3.75 mg of the test medications. Incremental doses (25% in initial dose) were administered, if necessary, until the patient's speech became thickened and slurred but the patient was still responsive to verbal commands. When needed, additional doses were administered to maintain sedation.

Results

Deviations from Protocol

Two patients, one in each treatment group, were excluded from efficacy analyses. One patient experienced hypotension and apnea 10 minutes after receiving midazolam (0.095 mg/kg). This patient required respiratory assistance and the administration of Narcan to reverse the effects of meperidine and midazolam. Bronchoscopy was cancelled. Recovery was complete in 45 minutes. Patient who received diazepam (0.054 mg/kg), experienced laryngospasms due to edema from chronic bronchitis which forced the cancellation of the bronchoscopy.

Three patients did not answer questions on the 24-hour questionnaire:

- (Midazolam) - Recall of two-hour Trieger Test
- (Diazepam) - Recall of one and two-hour Trieger Test
- (Diazepam) - Recall Baseline Trieger Test

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Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.036 mg/kg of midazolam and 0.093 mg/kg of diazepam. An additional dose to maintain sedation was required by six midazolam-treated patients (22) and five diazepam-treated patients. The mean time required to reach the sedative end point (slurred speech) was similar in both groups (midazolam: 2.95 minutes, diazepam: 3.28 minutes) for similar mean duration of bronchoscopy.

Physician's Assessment of Sedation

The physician's assessment of sedation was in most instances "fair" to "excellent" for both midazolam and diazepam-treated patients. There were no significant differences between treatments in the physician's assessment of the test medications.

Patient's Assessment of Sedation

One hour after the procedure 8 of 9 midazolam patients and 9 of 10 diazepam patients rated the sedation as "good" or excellent, with one patient in each group rating it "fair." On the day following the procedure all patients rated the sedation produced by midazolam or diazepam as "good" or "excellent." Both groups reported the procedure as "somewhat painful" or "not painful," although 6 of 9 midazolam patients reported no pain versus 9 of 10 diazepam patients. Eight of nine midazolam patients indicated they would elect to undergo the procedure the same way again, one hour after the procedure as well as on the following day; while, 9 of 10 diazepam patients would elect the same method of sedation one hour after the procedure and 10 of 10, the following day.

Trieger Test

Diazepam-treated patients missed significantly more dots on the one and two-hour than did midazolam-treated patients. Total deviation from dots (mm) was also significantly greater among the diazepam-treated patients at the two-hour testing time.

Follow-up Questionnaire for Amnesia

There were no significant differences between treatments with respect to any of the recall questions. Recall of bronchoscopy was present in 1/9 midazolam patients and 4/10 diazepam patients.

Most patients, on the following day, had no retrograde amnesia as evidenced by recall of the baseline Trieger Test, the injection in the thigh and the spraying of the throat. Anterograde amnesia with respect to recall of scope introduction and withdrawal was induced in the majority of patients in both groups. This amnesia extended for two hours for 3/9 patients in the midazolam group and 5/10 patients in the diazepam group with respect to recall of the post-treatment Trieger Tests.

000033

G. Adverse Reactions

Severe Reactions

Patient - Midazolam

A 72 year old female with a history of hypertension developed hypotension and apnea 10 minutes after receiving 1.25 ml (0.095 mg/kg) of midazolam. The patient required artificial ventilation for 25 minutes. A drop in blood pressure from 190/100 mmHg to 130/80 mmHg was observed. Narcan was administered to reverse the hypotension induced by meperidine and midazolam. Recovery was complete within 45 minutes; however, the bronchoscopy was cancelled. The investigator attributed the hypotension and apnea to both the meperidine and midazolam.

Patient - Diazepam

A patient with chronic obstructive pulmonary disease experienced momentary apnea. This did not require any intervention; consequently, the procedure was successfully completed.

Patient - Midazolam

This patient displayed clenching of the jaws twice during the administration of a local anesthetic agent to the pharynx and once immediately following the intravenous injection of midazolam. After 1 1/2 to 2 minutes the jaws relaxed and the procedure could be continued. Since the clenching of the jaws was observed first before the administration of midazolam, the investigator felt that this was only remotely related to the administration of midazolam.

Patient - Diazepam

This patient experienced laryngospasm which prevented bronchoscopic passage, forcing cancellation of the bronchoscopy. The laryngospasm was felt to be caused by marked edema of the pharynx due to chronic bronchitis. There was no venous irritation in any patient at the time of follow-up examination.

Changes in Vital Signs

The following tables indicate in which phase of the study the changes in vital signs occurred and the severity of the changes. Most changes were mild to moderate and were most often associated with the bronchoscopy.

000035

Table 3

Changes From Baseline For Respiration Rate

	Number of Patients	
	Midazolam	Diazepam
<u>Number of Patients Studied</u>	10	11
<u>During Induction of IV Sedation</u>		
Decrease	-	1
<u>During Bronchoscopy</u>		
Decrease (20-30%)	-	2
Decrease (30-50%)	4	3
Decrease ($\geq$ 50%)	-	2
Increase (20-30%)	1	1
Increase (30-50%)	2	4
Increase ($\geq$ 50%)	2	1
<u>During Recovery</u>		
Decrease (20-30%)	3	1
Decrease (30-50%)	1	4
Increase (20-30%)	2	2
Increase (30-50%)	1	1
Increase ($\geq$ 50%)	1	-

Summary and Conclusions

Although this randomized, double-blind study only involved 21 patients, it demonstrated that midazolam and diazepam were both effective intravenous sedative agents for bronchoscopy, when used in combination with meperidine and a topical anesthetic agent. Favorable ratings for sedation were given by the physician and patients in both groups. Diazepam-treated patients had a significant increase in number of dots missed and total deviation from dots in the Trieger Test, indicating possible impairment of psychomotor performance following the procedure. Both agents were effective in producing retrograde amnesia and amnesia for scope manipulation.

Apnea and hypotension was experienced by a midazolam patient, and momentary apnea was experienced by one diazepam patient. There were no reports of irritation at the intravenous injection site at the follow-up examination. Most changes in vital signs were not clinically significant.

This study showed that midazolam, when used in combination with meperidine and a topical anesthetic agent was as safe and effective as diazepam in inducing sedation for bronchoscopy. It was as useful as diazepam in producing retrograde failure of recall and certain aspects of antegrade failure of recall.

000036

Study No. 118

Title: A Comparison of Midazolam and Diazepam In Combination With Meperidine During Local Anesthesia for Bronchoscopy

Investigator: Stephen Jenkinson, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in adults undergoing bronchoscopy for the first time.

Experimental Design

Randomized, double-blind study in 21 adults undergoing bronchoscopy. The design of this study was similar to that of study 117 since this was a multicenter study following the same protocol.

Subjects

There were 9 non-pregnant females and 12 males ranging in age from 27 to 70 years. In the midazolam group there were 5 males and 5 females with a mean age of 53.4 years (range 27-70). In the diazepam group there were 7 males and 4 females with a mean age of 48.3 years (range 33-67).

Study Drugs: See Study 117.

Results

Deviations from Protocol

Patients | who received midazolam, was excluded from all efficacy analyses since this was the second time a bronchoscopy had been done. This patient had been previously entered in the study as patient This patient was included in all safety analyses.

One patient | who received midazolam could remember doing the Trieger Test only once following the bronchoscopy but did not know whether it was the one or two-hour test. The responses to recall of the Trieger Test, therefore, were not included in the analysis.

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.096 mg/kg of midazolam and 0.006 mg/kg of diazepam. The mean time to reach the sedative end point (slurred speech) was similar in both groups (midazolam: 3.94 minutes, diazepam; 4.58 minutes) for similar mean durations of bronchoscopy.

000037

Physician's Assessment of Sedation

The physician's assessment of sedation was in most instances "good" to "excellent" for both midazolam and diazepam-treated patients. Patients in the midazolam group had significantly better tolerance of the procedure than did patients in the diazepam group. There were no other significant differences between ten groups in the other assessments.

Patient's Assessment of Sedation

One hour after the procedure, all patients in the midazolam group rated the quality of sedation as "good" or "excellent" (9/9) which was significantly better than the rating by patients in the diazepam group (8/11) with 2 patients in this group rating "fair" and 1, "poor." There was no significant difference on the following day since two diazepam-treated patients changed their opinion of the quality of sedation from "fair" to "good." All of the midazolam and 9 of 11 diazepam patients indicated they would elect to undergo the procedure the same way again, one hour after the procedure as well as on the following day. Eight of nine midazolam patients reported no pain associated with bronchoscopy compared with 10 of 11 diazepam patients.

Trieger Test

There were no significant differences between groups in number of dots missed and total deviation from dots (mm).

Follow-Up Questionnaire for Amnesia

With respect to the questions for retrograde amnesia 3 of 9 midazolam patients and 11 of 11 diazepam patients had clear recall of the baseline Trieger Test. Five of 9 midazolam patients and 11 of 11 diazepam patients had clear recall of the injection in the thigh of meperidine. These differences were statistically significant and indicate more retrograde amnesia for midazolam patients. There was also some antegrade amnesia in midazolam patients since all but one did not have clear recall of scope introduction compared with only 3 of 11 diazepam patients. This difference was statistically significant. Four of 9 midazolam patients had antegrade amnesia extending to two hours with respect to failure to recall the post-treatment Trieger Test, compared with 1 of 11 diazepam patients.

Safety

Patient II - Diazepam A 67 years old male with a history of coronary artery disease experienced anginal pains at the end of the procedure. The pains were relieved by the administration of nitroglycerin.

No patient in either group had evidence of venous irritation at the follow-up examination.

000038

Changes in Vital Signs

The following table indicates in which phase of the study the changes in vital signs occurred and the severity of the changes. Most changes were associated with the bronchoscopy. No changes in vital signs were observed during the period of induction of sedation. Severe increases in respiration and pulse rate were observed in several patients in both treatment groups.

Table 1

Changes From Baseline For Vital Signs

<u>Number of Patients Studied</u>	<u>Number of Patients</u>	
	<u>Midazolam</u>	<u>Diazepam</u>
	10	11
<u>Respiration Rate</u>		
<u>During Bronchoscopy</u>		
Decrease (20-30%)	1	-
Decrease (30-50%)	-	1
Increase (20-30%)	-	4
Increase (30-50%)	-	2
Increase ($\geq$ 50%)	2	1
<u>During Recovery</u>		
Decrease (20-30%)	1	-
Increase (30-50%)	2	2
Increase ($\geq$ 50%)	2	2
<u>Pulse Rate</u>		
<u>During Bronchoscopy</u>		
Decrease (20-30%)	-	1
Increase (30-50%)	1	2
Increase ($\geq$ 50%)	1	1
<u>During Recovery</u>		
Decrease (20-30%)	1	1
Increase (20-30%)	1	2
Increase (30-50%)	-	1
Increase ($\geq$ 50%)	2	-
<u>Mean Arterial Pressure</u>		
<u>During Bronchoscopy</u>		
Increase (20-30%)	-	2

000039

Summary and Conclusions

This randomized, double-blind study in 21 patients demonstrated that midazolam and diazepam were both effective intravenous sedative agents for bronchoscopy, when used in combination with meperidine and a local anesthetic agent. Favorable ratings for sedation were given by the physician and patients in both groups. Most patients reported little or no pain associated with the bronchoscopy and were willing to undergo the procedure the same way again, if necessary. One hour following the procedure, quality of sedation was rated as significantly better by the midazolam patients.

Amnesia for certain events prior to drug administration (baseline Trieger Test, thigh injection) was significantly more frequently observed in the midazolam patients as was amnesia, after drug administration, for recall of scope introduction. Recovery from sedation as assessed by the Trieger Test was comparable between treatments.

Changes in vital signs were comparable between groups and were not felt to be clinically significant. At the follow-up examination, no patient had evidence of venous irritation. One diazepam patient, with a history of coronary artery disease, experienced anginal pains at the end of the procedure which were relieved by nitroglycerine.

Midazolam was shown in this study to be a useful sedative agent when used in combination with meperidine and a topical anesthetic agent. It was comparable to diazepam with respect to safety and effectiveness and was superior with respect to production of certain aspects of retrograde and anterograde amnesia.

000040

Study No. 123

Title: A Comparison of Midazolam and Diazepam In Combination With Meperidine During Local Anesthesia for Bronchoscopy

Investigator: William I. Mariencheck, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in adults undergoing bronchoscopy for the first time.

Experimental Design

Randomized, double-blind study in 24 adults undergoing bronchoscopy. The design of this study was similar to that of study 117 since this was a multicenter study following the same protocol.

Subjects

There were 12 non-pregnant females and 12 males ranging in age from 20 to 79 years. In the midazolam group there were 4 males and 7 females with a mean age of 48.1 years (range 25-72). In the diazepam group there were 8 males and 5 females with a mean age of 53.4 years (range 20-79).

Study Drugs: See Study 117.

Results

Deviations from Protocol

These patients were excluded from the efficacy analyses only.

- Patient - Diazepam: The drug was not administered according to protocol. 8 mls of drug was given without using "slurred speech" as an index for dosage.
- Patient - Midazolam: Excludable concomitant medication (Asendin) was given within 24 hours of the procedure.
- Patient - Midazolam: Excludable concomitant medication (Valium) was given within 24 hours of the procedure.

There were only 11 diazepam-treated patients evaluated for amnesia since Patient [redacted] did not return the 24-hour follow-up questionnaire. This patient's Trieger Test results were also excluded from analysis since meperidine and atropine were administered before the baseline Trieger Test was done. Patient #8 of the midazolam group did not do the baseline Trieger Test; therefore, the post-treatment Trieger Test results were excluded from analysis.

000041

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.132 mg/kg of midazolam and 0.155 mg/kg of diazepam. The mean time to reach the sedative end point (slurred speech) was similar in both groups (midazolam: 3.06 minutes, diazepam: 2.58 minutes) for similar mean durations of bronchoscopy.

Physician's Assessment of Sedation

The physician's assessment of sedation was in most instances "good" to "excellent" in both treatment groups, with the exception of control of cough reflex which was rated "fair" to "good" in both groups. There were no statistically significant differences between treatments in the physicians assessment of the test medications.

Patient's Assessment of Sedation

On both assessment occasions (one hour after the procedure and on the following day) patients rated the quality of sedation significantly better than diazepam-treated patients. Both test groups reported little or no pain associated with the bronchoscopy.

All midazolam and most diazepam-treated patients indicated that they would elect to have a future bronchoscopy done the same way.

Trieger Test

There were no significant differences between groups in psychomotor recovery from sedation. Midazolam-treated patients returned to baseline values for number of dots missed and deviation from dots after two hours; whereas, diazepam-treated patients increased from their baseline values at both one and two hours.

Follow-Up Questionnaire for Amnesia

All patients in both groups recalled the baseline Trieger Test, the meperidine injection and the topical anesthetic spraying prior to bronchoscopy indicating lack of retrograde recall. Following intravenous drug administration, recall of the introduction and withdrawal of the bronchoscope was absent in all of the midazolam and all but 1 of the diazepam patients. The sponsor erroneously referred to the instrument used as a "cystoscope" on page 8 of the summary. Several patients in both groups could not recall the one-hour post-treatment Trieger Test. All patients could recall the two-hour post-treatment Trieger Test.

000042

Safety

Immediately following injection of midazolam patient experienced mild hiccoughs which subsided spontaneously after 15-30 seconds. Two midazolam patients experienced nausea following the bronchoscopy. One diazepam patient developed nausea and vomiting following the procedure while patient had nausea upon injection of diazepam. During injection of diazepam, four patients experienced pain. Only patient #20 had subsequent evidence of venous irritation (tenderness, redness) which subsided after 2 days. No treatment was required for any of the adverse experiences.

Changes in Vital Signs

The following table indicates in which phase of the study the changes in vital signs occurred and the severity of the changes. Most changes were mild to moderate and were most often associated with the bronchoscopy. Only one change occurred during induction. Patient who received midazolam had a mild increase in respiration rate.

Table 1

Changes From Baseline In Vital Signs

<u>Number of Patients Studied</u>	<u>Number of Patients</u>	
	<u>Midazolam</u>	<u>Diazepam</u>
	11	13
<u>Mean Arterial Pressure</u>		
<u>During Bronchoscopy</u>		
Decrease (20-30%)	1	-
Increase (20-30%)	1	3
<u>During Recovery</u>		
Decrease (20-30%)	-	1
Decrease (30-50%)	1	-
Increase (20-30%)	-	1
<u>Pulse Rate</u>		
<u>During Bronchoscopy</u>		
Decrease (20-30%)	-	4
Increase (30-50%)	1	4
Increase ($\geq$ 50%)	3	-

000042

Table 1 (Continued)

	Number of Patients	
	Midazolam	Diazepam
<u>Pulse Rate (Continued)</u>		
<u>During Recovery</u>		
Decrease (20-30%)	3	1
Increase (20-30%)	1	6
Increase (30-50%)	1	2
Increase ($\geq$ 50%)	2	-
<u>Respiration Rate</u>		
<u>During Induction</u>		
Increase (20-30%)	1	-
<u>During Bronchoscopy</u>		
Decrease (20-30%)	-	1
Decrease (30-50%)	1	-
Increase (20-30%)	1	3
Increase (30-50%)	1	1
Increase ($\geq$ 50%)	1	-
<u>During Recovery</u>		
Decrease (20-30%)	1	-
Decrease (30-50%)	1	2
Increase (20-30%)	1	2
Increase (30-50%)	1	1
Increase ($\geq$ 50%)	2	2

Summary and Conclusions

This randomized, double-blind study included 24 patients and demonstrated that both midazolam and diazepam were effective intravenous sedative agents for bronchoscopy when used as adjuncts to intramuscular meperidine and local anesthetic. Assessment of sedation by the physician was "good" to "excellent" for all parameters of both test medications except for control of cough reflex which was classified as "fair" to "good." Midazolam patients rated the quality of sedation significantly better than diazepam patients. All midazolam patients and diazepam patients indicated that they would elect to undergo the procedure the same way again.

Recall of the bronchoscopic procedure was absent in all of the midazolam and all but one of the diazepam patients. Both test groups showed some psychomotor impairment one hour following the bronchoscope. This persisted at the two-hour assessment in the diazepam-treated patients.

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Changes in vital signs were not felt to be clinically significant. Two patients in each group experienced nausea and one diazepam-treated patient also experienced vomiting. On injection of midazolam one patient experienced mild hiccoughs which promptly subsided. The investigator felt that the nausea, vomiting and hiccoughs were possibly related to the administration of midazolam and diazepam. No treatment was required for any adverse experiences. Four patients experienced pain upon injection of diazepam; however, only one of these patients had evidence of venous irritation (tenderness and redness) on the follow-up examination. No midazolam patients had evidence of venous irritation.

In this study midazolam was shown to be a useful sedative agent when used in combination with meperidine and a topical anesthetic agent. It was as safe and effective as diazepam in inducing sedation for bronchoscopy. The use of both agents was associated with diminished recall of the procedure.

Pooled Study Summary

Study No. 105, 113, 119, 150, Protocol 2236A

Title A Comparison of Midazolam and Diazepam Administered Intravenously With Local Anesthesia For Cystoscopy

Subjects

One hundred fifty-one patients (ASA Status I or II) undergoing diagnostic cystoscopy for the first time participated in the study. The study populations consisted of 42 non-pregnant females and 109 males ranging in age from 17 to 86 years. In the midazolam group there were 75 patients comprised of 54 males and 21 females with a mean age of 52.2 years (range 17-86). In the diazepam group there were 76 patients comprised of 55 males and 21 females with a mean age of 49.3 years (range 18-85).

ResultsDifferences Between Study Centers

There was a difference by centers in initial dose of the test drug for induction of sedation. In Dr. Evan's study (#113), patients receiving midazolam required a higher dose than did those who received diazepam. At the other three study sites the dose of diazepam was greater than midazolam.

There was a difference between study centers on the physician's assessment of sedation. Dr. Evans rated diazepam patients higher on all sedation parameters. The investigators at the other three centers either rated patients who received midazolam as better sedated or rated the sedative effects of the two test drugs as comparable.

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.152 mg/kg of midazolam and 0.170 mg/kg of diazepam. Two patients in Dr. Evan's study (one in each treatment group) required a maintenance sedation dose for completion of the procedure. The mean time to reach the sedative end point was 3.9 and 3.5 minutes respectively in the midazolam and diazepam groups. The mean length of the procedures was comparable between treatment groups.

Physician's Assessment of Sedation

There were no significant differences between treatments. All parameters were rated "good" to "excellent."

Patient's Assessment of Sedation

On two occasions patients assessed the sedative effects of the test drugs and whether they were willing to undergo a future procedure the same way. The two assessment periods were one hour after the procedure and on the following day. On both occasions quality of sedation was rated significantly better by midazolam-treated patients.

On both occasions ninety percent or more of the patients in both treatment groups were willing to have a future procedure done the same way. At the 24 hour interval significantly more midazolam patients were willing to have the procedure done the same way. They also reported significantly less pain associated with the cystoscopy.

Trieger Test

At one hour the increase in number of dots missed and deviations from the dots was significantly greater for patients treated with midazolam. By two hours both treatment groups had returned to near the baseline values.

Follow-up Questionnaire for Amnesia

While most patients could recall completing the baseline Trieger Test prior to test drug administration significantly more of the patients who received midazolam could not recall the administration of the local anesthetic agent.

Following test drug administration, one hour after the procedure, the diazepam group had little diminution in recall of cystoscopy; where, the midazolam group had significantly less recall. In this group there was also significantly less recall of the introduction and withdrawal of the scope as well recall of the one and two hour Trieger Tests, when questioned on the following day. Incidence of recall for the scope was much less than for the Trieger Tests.

Safety

Table 1

Clinical Adverse Experiences

<u>Possibly and Probably Related Drug Effects</u>	<u>Midazolam</u>		<u>Diazepam</u>	
	<u>No. Pts.</u>	<u>Percent</u>	<u>No. Pts.</u>	<u>Percent</u>
<u>Respiratory System</u>				
Respiration Rate Increase	15	20.0	14	18.4
Respiration Rate Decrease	12	16.0	8	10.5
Shallow Respiration	1	1.3	0	0
Apnea	1	1.3	3	3.9
<u>Cardiovascular System</u>				
Pulse Increase	12	16.0	12	15.8
Pulse Decrease	6	8.0	5	6.6
HAP Increase	3	10.7	3	3.9
HAP Decrease	12	16.0	4	5.3
Hypotension	0	0	1	1.3
Tenderness of Vein	3	4.0	1	1.3
Redness of Vein	1	1.3	0	0
Induration of Vein	2	2.7	1	1.3
<u>Miscellaneous</u>				
Excessive Sedation	1	1.3	0	0
<u>Remotely Related Effects</u>				
Arrhythmia	0	0	1	1.3

Changes in vital signs were observed more frequently during and following the cystoscopy than during induction of sedation. Most changes were classified as mild or moderate.

Summary and Conclusions

In this multicenter study the results of four randomized, double-blind, parallel group studies included 151 patients undergoing diagnostic cystoscopy for the first time. It was demonstrated that midazolam and diazepam were effective intravenous sedative agents for cystoscopy when used as adjuncts to local anesthetic. Sedation was achieved with mean doses of 0.152 mg/kg of midazolam and 0.170 mg/kg of diazepam in a mean time of less than 4 minutes for both treatment groups.

The physicians' assessment showed no intergroup difference, but the patients rated the quality of sedation significantly better and reported significantly less pain associated with the cystoscopy. Furthermore, significantly more midazolam patients were willing to have the procedure done the same way in the future.

The Trieger Test was used to assess the recovery from sedation. One hour after the procedure midazolam patients had significantly more impairment of psychomotor performance; however, by two hours both treatment groups were approaching complete recovery from the sedative effects of the drugs.

Midazolam patients had significantly less recall of the local anesthetic agent as well as recall of cystoscopy and recall of the postoperative Trieger Tests.

Four patients at one study Center (#150), one of whom received midazolam and three who received diazepam, experienced momentary apnea following induction of sedation. No corrective measures were required and all procedures were successfully completed.

One patient had shallow respiration after receiving midazolam (0.169 mg/kg). Another patient who received midazolam (0.134 mg/kg) experienced excessive sedation following the procedure.

One diazepam-treated patient developed hypotension which was attributed to the drug's sedative effects. Three midazolam patients and one diazepam patient had evidence of venous irritation on the follow-up examination.

This study showed that IV midazolam was safe as diazepam and was considered by the patients to be more effective than diazepam in inducing sedation for cystoscopy. Patients who received midazolam experienced less pain (not no pain, as stated by the sponsor) and had diminished recall of the procedure.

000019

Study No. 105

Title: A Comparison of Midazolam and Diazepam Administered Intravenously With Local Anesthesia for Cystoscopy

Investigator: Russell Lawson, M.D.

Objective: The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in patients undergoing cystoscopy for the first time.

Experimental Design

Randomized, double-blind study in 43 adults undergoing cystoscopy for the first time. The design of this study was similar to that of study 150 since this was a multicenter study following the same protocol.

Subjects

There were 24 non-pregnant females and 19 males ranging in age from 18 to 86 years. In the midazolam group there were 9 males and 13 females with a mean age of 49.6 years (range 18-86). In the diazepam group there were 10 males and 11 females with a mean age of 48.3 years (range 19-85).

Study Drugs See Study 150.

Results

Deviations from Protocol

Two patients | who received diazepam were excluded from all efficacy analyses due to protocol violations. Both patients were ASA status III, while the protocol called for status I-II. Patient , a 77 year old male, received 0.062 mg/kg of diazepam. Patient , an 84 year old female, received 0.065 mg/kg of diazepam. No side effects were observed and these patients were included in all safety analyses.

Due to delays encountered during the induction period, the time to induction was not recorded for one patient in each treatment group. For patient the procedure was delayed after administration of 5 mg of diazepam due to difficulties with the cystoscope; therefore an additional 5 mg of drug was required to maintain sedation. In the case of patient following administration of 10 mg of midazolam, a slight increase in blood pressure was observed. The procedure was delayed while the patient was observed for several minutes; however, since adequate sedation was not reached, an additional 5 mg of midazolam was administered. One patient , who received 0.128 mg/kg of midazolam, could not do the one-hour Trieger Test due to excessive sedation.

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Induction of Intravenous Sedation

Comparable levels of sedation were obtained with mean doses of 0.117 mg/kg of midazolam and 0.131 mg/kg of diazepam. The average time required to reach the sedative end point (slurred speech) for midazolam and diazepam were 2.50 minutes and 3.90 minutes. The duration of cystoscopy was similar for both groups.

Physician's Assessment

The physician's assessment of sedation was in most instances "good" to "excellent" for patients in both groups. Muscle relaxation, control of bladder spasm and control of pain ratings were significantly better in the midazolam group.

Patient's Assessment

One hour following the cystoscopy, all patients rated the quality of sedation as "good" or "excellent." Significantly more midazolam-treated patients rated sedation as "excellent" compared with diazepam-treated patients. On the following day no significant difference between treatments was found since patients in both groups changed their evaluations. While midazolam-treated patients reported significantly less pain associated with the cystoscopy, all patients in both groups indicated they would elect to undergo the procedure the same way again, with the exception of the midazolam group one hour after the procedure, when 91% responded affirmatively.

Trieger Test

There were no statistically significant differences between groups with respect to recovery from sedation. Midazolam-treated patients had a higher number of dots missed and total deviations from the dots one hour following the cystoscopy. At two hours the results in both groups were returning toward the baseline values.

Follow-Up Questionnaire for Amnesia

One hour after the procedure, both treatment groups had diminished recall of the cystoscopy. Midazolam-treated patients had significantly less recall of the procedure. By the following day, the majority of patients in both groups had diminished recall of scope introduction and withdrawal; however, recall was less in the midazolam group.

While most patients could recall doing the baseline Trieger Test prior to test drug administration, 32% of the diazepam group and 59% of the midazolam group had no recall of the administration of local anesthesia. The majority of patients in both groups had recall of the post-treatment Trieger Tests.

000051

Safety

a 66 year old male diabetic, experienced arrhythmias and a drop in blood pressure after receiving 0.142 mg/kg of diazepam. The patient was hypertensive before receiving diazepam and was still hypertensive following a drop in blood pressure from 192/127 mmHg to 171/104 mmHg. The drop in blood pressure was attributed to the sedative effects of diazepam. Since the arrhythmias were observed both before and during the cystoscopy, the investigator felt that the arrhythmias were remotely related to diazepam. No corrective treatment was required for either adverse experience. Patient #40, who received diazepam, experienced tenderness and redness at the injection site for 3 days following the study.

A 69 year old male experienced excessive sedation after receiving 0.134 mg/kg of midazolam. The investigator was unable to arouse the patient at one hour to do the Trieger Test except by painful stimuli.

Three midazolam-treated patient experienced venous irritation at the injection site following the study. Patient experienced tenderness, redness and induration for two days. Patient experienced tenderness for 5 days. Patient experienced tenderness and induration for 3 days.

Most changes in vital signs were transient and were most often associated with the cystoscopy. Few changes in vital signs were observed during induction.

Summary and Conclusions

This randomized, double-blind study compared the use of IV midazolam with IV diazepam to provide sedation during cystoscopy. These agents were used as adjuncts to local anesthesia provided by topical lidocaine. Assessment of sedation by the physician was "good" to "excellent" for both medications. No consistent difference was observed between groups with respect to patient assessment of the quality of sedation. Midazolam-treated patients reported significantly less pain associated with the procedure, but all patients in both groups indicated, by the following day, that they would undergo a future cystoscopy the same way. There were no significant differences between treatments on the Trieger Test, but midazolam patients had greater impairment of psychomotor performance one hour after the procedure.

Both groups of patients had diminished recall of the cystoscopy. One hour after the procedure the midazolam group had significantly less recall than the diazepam group; however, on the following day no significant differences between treatments were observed. The majority of patients in both groups had recall of the post-treatment Trieger Tests.

A 66 year old hypertensive diabetic patient experienced a drop in blood pressure after receiving diazepam. This drop was attributed to a sedative effect. The patient also experienced arrhythmias before and during the cystoscopy. The investigator felt the arrhythmias were remotely related to diazepam administration.

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A 69 year old midazolam-treated patient experienced excessive sedation after the cystoscopy and was aroused with painful stimuli. This may have been age and dose-related (0.134 mg/kg).

One diazepam and three midazolam-treated patients experienced venous irritation at the injection site following the study. Transient changes in vital signs were noted in both groups but were not considered clinically significant.

This study showed that midazolam, when used in combination with a local anesthetic agent (lidocaine) is as safe and effective as diazepam in inducing sedation for cystoscopy. Midazolam treatment was associated with less procedural pain and less recall of the procedure after one hour.

A 69 year old male experienced excessive sedation after receiving 10 mg of midazolam for sedation during cystoscopy.

The patient was brought back to the operating room and aroused with painful stimuli. The patient was given 100% oxygen and 10 mg of flumazenil, which resulted in complete arousal. The patient was discharged home without incident.

The sedation was considered to be age and dose related.

This study compared the sedative effects of midazolam and diazepam for cystoscopy. Both drugs were found to be effective in inducing sedation. Midazolam was associated with less procedural pain and less recall of the procedure after one hour. The study also showed that midazolam, when used in combination with a local anesthetic agent (lidocaine) is as safe and effective as diazepam in inducing sedation for cystoscopy.

The results of this study suggest that midazolam is a safe and effective sedative for cystoscopy. It is associated with less procedural pain and less recall of the procedure after one hour compared to diazepam.

Study No. 113

Title: A Comparison of Midazolam and Diazepam Administered Intravenously With Local Anesthesia for Cystoscopy

Investigator: Arthur T. Evans, M.D.

Objective: The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in patients undergoing cystoscopy for the first time.

Experimental Design

Randomized, double-blind study in 28 patients undergoing cystoscopy for the first time. Forty patients were required by the protocol and this is an interim report of an in-progress study. The design of this study was similar to that of study 150 since this was a multicenter study following the same protocol.

Subjects

There were 9 non-pregnant females and 19 males (ASA status I or II) ranging in age from 17 to 54 years. In the midazolam group there were 10 males and 3 females with a mean age of 32.2 years (range 17-54). In the diazepam group there were 9 males and 6 females with a mean age of 27.7 years (range 19-47).

Study Drugs: See study 150.

Results

Deviations from Protocol

A 19 year old male patient was excluded from efficacy analysis for receiving an excludable concomitant medication within 24 hours of the procedure. After receiving 0.169 mg/kg of diazepam, the patient admitted to having smoked some marijuana on the morning of the procedure. This patient was included in all safety analyses.

One midazolam-treated patient was only 17 years old which was a protocol deviation. This patient was, however, included in all efficacy and safety analyses.

The 24 hour questionnaires of two midazolam patients were not included in the efficacy analysis. Patient answered the questionnaire on the same day as the procedure. Patient did not return the questionnaire.

Several questions were not answered by three patients on the 24 hour questionnaire:

(midazolam) Recall One-hour Trieger Test
 (diazepam) Recall Two-Hour Trieger Test
 (This patient did not do the two-hour Trieger Test)
 (diazepam) Recall Two-Hour Trieger Test

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.209 mg/kg of midazolam and 0.175 mg/kg of diazepam. An additional dose to maintain sedation was required by one patient in each treatment group. Although there was no significant difference in the mean times required to reach the sedative end point, the midazolam group took almost twice as long. The duration of the cystoscopy was similar for both groups.

Physician's Assessment

The physician's assessment of sedation was "fair" to "excellent" for both midazolam and diazepam treatment groups. Control of bladder spasm and quality of sedation were rated significantly higher in the diazepam group.

Patient's Assessment

One hour after the procedure most patients in both treatment groups rated sedation as "good." On the following day significantly more patients in the midazolam group rated sedation as "excellent" or "good" than the diazepam-treated patients. Both treatment groups reported little or no pain associated with the procedure. Most patients in both groups would undergo the procedure the same way again.

Trieger Test

There were no significant differences between groups in recovery from sedation. Both groups had an increase from baseline in number of dots missed and total deviation from the dots one hour following cystoscopy. At two hours the results had returned close to the baseline value.

Follow-Up Questionnaire for Amnesia

All patients in both treatment groups could recall the baseline Trieger Test. Significantly more midazolam patients had no recall of local anesthesia. Midazolam-treated patients also had significantly less recall of the introduction and withdrawal of the cystoscope and the one hour post-treatment Trieger Test. There was no significant differences between groups in recall of the two hour Trieger Test.

Safety

A 33 year old female patient experienced shallow respiration 2 minutes after receiving 10 mg (0.169 mg/kg) of midazolam. She was given oxygen and breathing was assisted with an Ambu bag for 30 minutes. No additional complications were observed and the patient was able to leave the hospital at the end of the study procedure. The investigator felt that the shallow respiration was caused by the administration of too high a dose of midazolam to the patient.

Very few changes in vital signs were observed during the study. All changes were classified as mild or moderate and, with the exception noted above, were considered clinically insignificant.

No patient in either treatment group had evidence of venous irritation at the injection site following the study.

Summary and Conclusions

This randomized, double-blind study compared the use of IV midazolam with IV diazepam to provide sedation during cystoscopy. These agents were used as adjuncts to local anesthesia provided by topical lidocaine. This study was analyzed while still in progress and the interim report represents the results of the first 28 patients. As adjuncts to local anesthesia, both midazolam and diazepam were effective intravenous sedative agents for cystoscopy. Assessments of sedation by the physician were "fair" to "excellent" for all parameters. On the day following the procedure, quality of sedation was rated significantly better by midazolam-treated patients. All patients reported little or no pain associated with the cystoscopy and most patients in both groups were willing to undergo the procedure the same way again, if necessary.

Recovery from sedation as assessed by the Trieger Test was comparable between treatments, with both test groups showing psychomotor impairment one hour following cystoscopy and return toward baseline at two hours. Midazolam-treated patients had significantly less recall of local anesthetic administration as well as introduction and withdrawal of the cystoscope and the one hour post-treatment Trieger Test.

Most changes in vital signs were transient and were not considered clinically significant. One patient developed shallow respirations after receiving midazolam. Breathing was assisted and oxygen was administered. The shallow respiration was attributed to the administration of too high a dose of midazolam for this patient. There were no reports of venous irritation following the study.

This incomplete study demonstrated that midazolam, when used in combination with a local anesthetic agent, is as safe and effective as diazepam in inducing sedation for cystoscopy. It proved useful in producing diminished recall of the procedure.

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Patient's Assessment

One hour after the cystoscopy and on the following day, when patients assessed the quality of sedation, midazolam was judged significantly better. The midazolam patients found the procedure painless; however, 60 percent of the diazepam-treated patients found the procedure "somewhat painful" or "very painful." All midazolam and 85% of the diazepam-treated patients indicated that they would undergo the procedure the same way again.

Trieger Test

One hour after cystoscopy, midazolam patients had a statistically significant increase in number of dots missed and total deviation from the dots compared with the diazepam group. No significant difference between treatments was observed for the two hour test results.

Follow-Up Questionnaire for Amnesia

On the follow-up questionnaire, midazolam-treated patients had significantly less recall for all events of the procedure, with the exception of the baseline Trieger Test, than did diazepam-treated patients. Significantly more midazolam-treated patients had no recall of the introduction and withdrawal of the cystoscope and of the one and two hour post-treatment Trieger Tests. Most diazepam-treated patients had recall of all events before and after test drug administration.

Safety

The only adverse experiences reported were mild to moderate changes in pulse rate and mean arterial pressure. No changes in vital signs were observed during induction of intravenous sedation. No patient in either group had evidence of venous irritation on the follow-up examination.

Summary and Conclusions

This randomized double-blind study compared the use of IV midazolam with IV diazepam to provide sedation during cystoscopy. These agents were used as adjuncts to local anesthesia provided by topical lidocaine. As Adjuncts to local anesthesia both midazolam and diazepam were effective intravenous sedative agents for cystoscopy. Assessments of sedation by the physician were in most instances "good" to "excellent" for both test medications. The quality of sedation was rated significantly better by midazolam patients. No midazolam-treated patients found the cystoscopy painful compared to the diazepam group, where 60% experienced some pain during the cystoscopy. All midazolam and most diazepam patients indicated they would elect to undergo the procedure the same way again.

000058

On the one hour Trieger Test, midazolam-treated patients had a statistically significant increase in number of dots missed and total deviation from the dots compared with the diazepam group, suggesting impairment of psychomotor performance. At two hours, the changes returned to near the baseline values. Failure of recall of events immediately prior to and following test drug administration was induced in most midazolam-treated patients, while most diazepam-treated patients could recall all of these events.

Transient fluctuations in blood pressure and pulse rate were noted, but were not felt to be clinically significant. There were no reports of venous irritation on the follow-up examination.

This study demonstrated that midazolam, when used in combination with a local anesthetic is as safe and effective as diazepam in inducing sedation for cystoscopy. Midazolam was more effective in inducing diminished recall of the procedure and other events before and after the procedure.

Study No. 150

Title: A Comparison of Midazolam and Diazepam Administered Intravenously with Local Anesthesia for Cystoscopy

Investigator: George Chasapakis, M.D.

Objective: The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in patients undergoing cystoscopy for the first time.

Experimental Design:

Randomized, double-blind study in 40 adults undergoing cystoscopy for the first time. Patients were randomly assigned to midazolam and diazepam treatment groups. Approximately 5 to 10 minutes before cystoscopy, lidocaine topical jelly was instilled into the urethra. Following this, 10-15 mg of either midazolam or diazepam was administered intravenously. Immediately following cystoscopy, the blinded physician, evaluated as excellent, good, fair or poor the sedative effects produced by the test medication. The assessments included: (1) patient cooperation, (2) muscle relaxation, (3) ease of cystoscopic examination, (4) quality of sedation, (5) control of bladder spasm, (6) control of pain, (7) control of retching and vomiting, (8) overall tolerance of the procedure. One hour after cystoscopy and one day later in a follow-up questionnaire, patients evaluated the sedation during the procedure as excellent, good, fair or poor. On both occasions patients were asked whether they would elect to undergo a future cystoscopy the same way. One hour after the procedure, patients evaluated the cystoscopy as not painful, somewhat painful or very painful and whether they could recall none, some or all of the cystoscopy. In the follow-up questionnaire, patients were also asked whether they could recall clearly, vaguely or not at all events before, during and after cystoscopy.

Recovery from sedation was assessed by the Trieger Test which was completed by the patient before medication (baseline) and at 1 and 2 hours after cystoscopy.

Blood pressure, respiratory rate and pulse rate were monitored before, during and after cystoscopy. Changes in vital signs greater than 20 percent from baseline were identified as possible adverse experiences. The severity of the change was categorized as follows:

Mild = a change $\geq$ 20 percent by $<$ 30 percent from baseline
Moderate = a change $\geq$ 30 percent but $<$ 50 percent from baseline
Severe = a change $\geq$ 50 percent from baseline or treatment required

Clinical adverse experiences were further categorized according to the phase of the study. The phases of the study were defined as follows:

induction = period of test drug administration
maintenance = period of cystoscopy
recovery = post cystoscopy until discharge.

000056

Study No. 119

Title: A Comparison of Midazolam and Diazepam Administered Intravenously With Local Anesthesia For Cystoscopy

Investigator: Alan J. Wein, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in patients undergoing cystoscopy for the first time.

Experimental Design

Randomized, double-blind study in 40 patients undergoing cystoscopy for the first time. The design of this study was similar to that of study 150 since this was a multicenter study following the same protocol.

Subjects

There were 40 males ranging in age from 40 to 76 years (ASA Studies I and II). In the midazolam group there were 20 patients with a mean age of 61.0 years (range 20-75). In the diazepam group there were 20 patients with a mean age of 55.7 years (range 34-76).

Study Drugs

See Study 150.

Results

Deviations from Protocol

One midazolam-treated patient did not understand the directions for the Trieger Test; therefore, this patient's data were not included in the Trieger-Test analysis. Patient of the midazolam group was unable to complete the one-hour Trieger Test because of excessive sedation.

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.118 mg/kg of midazolam and 0.140 mg/kg of diazepam. The mean time required to reach the sedative end point and the duration of cystoscopy were similar for both groups.

Physician's Assessment

The physician's assessment of sedation was in most instances "good" to "excellent" for both midazolam and diazepam-treated patients. The assessment of control of pain was significantly better for those patients who received midazolam. There were no statistically significant differences between treatments in the other assessments made by the physician.

Subjects

There were 9 non-pregnant females and 31 males ranging in age from 18 to 79 years (ASA Status I and II). In the midazolam group there were 15 males and 5 females with a mean age of 59.3 years (range 20-79). In the diazepam group there were 16 males and 4 females with a mean age of 60.1 years (range 18-76).

Study Drugs

Before cystoscopy, lidocaine topical jelly was instilled into the urethra. Following this, 10-15 mg of either midazolam or diazepam was administered intravenously over a 2-3 minute period. Elderly patients (as identified by the investigator) received 5-7.5 mg of the test medications. Incremental doses (25% of initial dose) were administered, if necessary, until the patient's speech became thickened and slurred but the patient was still responsive to verbal commands.

The formulation used in this study was not supplied by Hoffman-LaRoche, Nutley; however, it was a midazolam free base in a hydrochloric acid formulation. It was supplied by the company's Busle headquarters and appears to differ in that there is no edetate disodium in the formulation. In the opinion of this reviewer the formulations are not significantly dissimilar from a medical viewpoint.

Results

Deviations from Protocol

The seven to fourteen day follow-up examination of the intravenous injection site for tenderness, redness, or induration was not done on any patient in this study. One midazolam patient did not return the 24 hour patient questionnaire. Patient , who received diazepam (0.365 mg/kg) was extremely sleepy one hour following the procedure. This patient was unable to answer the one-hour questionnaire and to complete the one-hour Trieger Test. The physician did not answer the question of quality of sedation for patient of the diazepam group. Diazepam patient did not answer the question of pain associated with the cystoscopy.

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.164 mg/kg of midazolam and 0.234 mg/kg of diazepam. The respective mean times to reach the sedative end point (slurred speech) for midazolam and diazepam were 2.43 minutes and 3.03 minutes the average duration of the cystoscopies was similar for both groups.

Patients in both treatment groups performed well on their post-treatment Trieger Tests; however, diazepam-treated patients had a statistically significant increase in deviation from the dots at two hours compared with midazolam patients. While the majority of patients could recall the baseline Trieger Test, many could not recall the administration of local anesthesia. Failure to recall the introduction of the scope was induced in all of the midazolam patients and 95% of the diazepam patients. Failure to recall the withdrawal of the scope was induced in all patients.

Many patients experienced prolonged amnesia as they could not recall the one-hour post-treatment Trieger Test; however, most could recall the two-hour post-treatment test.

On midazolam and three diazepam-treated patients experienced momentary apnea following induction of sedation. However, since no corrective measures were required, all procedures were successfully completed. Transient changes in vital signs were observed in both treatment groups but were not felt to be clinically significant.

This study showed that midazolam, when used in combination with a local anesthetic agent, is as safe and effective as diazepam in inducing sedation for cystoscopy. Both midazolam and diazepam appear to be effective agents for inducing amnesia of the procedure.

Physician's Assessment

The physician's assessment of sedation was in most cases "good" to "excellent" for both midazolam and diazepam treatment groups. There were no statistically significant differences between treatments in the physician's assessment of the test medications.

Patient's Assessment

On two occasions (one hour after the procedure and the following day) most patients rated the sedation produced by both drugs as "good" or "excellent." Most patients in both groups reported little or no pain associated with the cystoscopy. Most patients were willing to undergo the procedure the same way again.

Trieger Test

Recovery from sedation was characterized in general by the fact that neither treatment group missed many dots or deviated far from the dots on the Trieger Test. At two hours, however, diazepam-treated patients had a statistically significant increase in deviation from the dots at two hours compared with midazolam-treated patients.

Follow-up Questionnaire for Amnesia

While almost all patients could recall the baseline Trieger Test, about half of the patients in both groups had no recall of local anesthesia administration. Most midazolam and diazepam-treated patients had no recall of the introduction and withdrawal of the introduction and withdrawal of the cystoscope on the following day, although one hour after the procedure most patients did recall the cystoscopy, with recall being greater in the diazepam group (55% vs. 79%). Most patients could recall the two-hour post treatment Trieger Test, although fewer patients in each group recalled the one-hour test.

Safety

One midazolam-treated patient (.161 mg/kg) and three diazepam-treated patients experienced apnea for 10-15 seconds following induction of sedation. No patient required corrective treatment and all cystoscopies were successfully completed. No changes in vital signs were observed during induction of sedation and all changes were classified as mild or moderate.

Summary and Conclusions

This randomized, double-blind study compared the use of IV midazolam with IV diazepam to provide sedation during cystoscopy. These agents were used as adjuncts to local anesthesia provided by topical lidocaine. Assessments of sedation by the physician and patient were "good" to "excellent" for both test medications. Most patients reported little or no pain associated with the procedure.

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Pooled Study Summary

Study Nos. 116, 126, Protocol 2237A

Title: A Comparison of Midazolam and Diazepam in Combination With
Heperidine During Local Anesthesia for Cystoscopy

Subjects

There were fifty female patients (ASA Status I or II) ranging in age from 21 to 88 undergoing diagnostic cystoscopy for the first time. There were 12 females in the midazolam group with a mean age of 52.4 years (range 28-98) and 13 in the diazepam group with a mean age of 45.4 years (range 21-80). In the midazolam placebo groups there were 13 females with a mean age of 45.1 years (range 21-72) and in the diazepam placebo groups there were 12 females with a mean age of 50.3 years (range 27-79).

Results

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.090 mg/kg of midazolam and 0.092 mg/kg of diazepam. Two midazolam and three diazepam-treated patients required a maintenance dose for completion of the procedure. The mean time to reach the sedative end points for both active drug groups was less than 3 minutes.

Physician's Assessment

The assessment for midazolam-treated patients was "excellent" for all parameters while assessments in the other groups ranged from "poor" to "excellent". Midazolam-treated patients were rated significantly better than placebo (midazolam) and diazepam patients on all assessments except for control of retching and vomiting.

Patient's Assessment

One hour after the procedure, midazolam-treated patients evaluated sedation as significantly better and reported significantly less pain during the procedure than did placebo (midazolam) patients. No other significant differences were noted.

Trieger Test

Midazolam-treated patients missed significantly more dots on the one and two hour Trieger Tests and had a significant increase in deviation from the dots at one hour compared with diazepam and placebo (midazolam) patients.

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Follow-Up Questionnaire for Amnesia

Significantly fewer midazolam-treated patients could recall receiving local anesthetic than placebo (midazolam) and diazepam patients. One hour after cystoscopy, significantly fewer midazolam than placebo patients had recall of the procedure and this difference was also true on the following day for not only placebo, but also for diazepam versus midazolam. The difference was extended through the two hour Trieger Test for midazolam and placebo.

Safety

One diazepam and one placebo (midazolam) patient experienced tenderness (burning) at the intravenous injection site during administration of the test drug. Neither patient had evidence of irritation at the injection site at the follow-up examination. One placebo (midazolam) patient experienced dizziness following premedication with meperidine. Transient changes in vital signs were observed in all four treatment groups. No changes were observed during induction of sedation. All changes were classified as mild or moderate. None of the changes were clinically significant.

Summary and Conclusions

In this pooled study at one center midazolam was used to provide sedation during cystoscopy. It was compared to diazepam and placebo when administered intravenously as an adjunct to meperidine and a topical anesthetic agent.

Comparable levels of sedation were attained with mean doses of 0.090 mg/kg of midazolam and 0.092 mg/kg of diazepam. The mean time to induce sedation was similar and under 3 minutes for both active treatment groups.

Midazolam was a more effective sedative agent than diazepam and placebo (midazolam) and was rated significantly better on all the physician's assessments except control of retching and vomiting.

Patients who received midazolam evaluated quality of sedation as significantly better and reported significantly less pain associated with the cystoscopy than did placebo (midazolam)-treated patients. There were no significant differences between the active treatments on these parameters.

Midazolam-treated patients apparently had residual sedative effects during the one and two hour Trieger Tests since they missed significantly more dots compared with diazepam-treated patients.

Failure of recall of the procedure was significantly greater for the midazolam than for the diazepam group as was failure to recall local anesthesia prior to induction.

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Transient fluctuations in vital signs were observed in all treatment groups but were not considered clinically significant. One diazepam and one placebo (midazolam)-treated patient experienced pain during the injection of the study drug. There were no reports of irritation at the intravenous injection site at the follow-up examination.

This study shows that midazolam, when used in combination with meperidine and lidocaine anesthetic, is as safe as diazepam in inducing sedation for cystoscopy. In this study the physician found midazolam to be a superior sedative agent and midazolam patients had more impairment of recall of the procedure and a pre-induction event than the diazepam group.

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Study No. 116

Title: A Comparison of Midazolam and Diazepam in Combination With Meperidine During Local Anesthesia for Cystoscopy

Investigator: Roy Witherington, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in 40 adult females undergoing cystoscopy for the first time.

Subjects

The study population consisted of 40 non-pregnant females (ASA Status I or II) ranging in age from 21 to 88 years. There were 10 females in each of 4 groups composed as follows:

1. Midazolam- mean age 52.4 years (range 28-88)
2. Diazepam- mean age 48.6 years (range 21-80)
3. Placebo (midazolam)- mean age 45.6 years (range 21-72)
4. Placebo (diazepam)- mean age 51.5 years (range 27-79)

Study Drugs

Approximately 30 minutes before cystoscopy, all patients received 25-50 mg of meperidine administered intramuscularly followed by the instillation of lidocaine topical jelly into the urethra 5 to 10 minutes prior to cystoscopy. Patients assigned to midazolam or diazepam treatment groups received 5.0-7.5 mg of the test medications intravenously over a 2-3 minute period. Elderly patients (as identified by the investigator) received 2.50-3.75 mg of the test medications intravenously over a 2-3 minute period. Incremental doses (25% of initial dose) were administered, if necessary, until the patient's speech became thickened and slurred but the patient was still responsive to verbal commands. Patients assigned to placebo groups received 1-3 ml total volume of solution administered intravenously over a 5 minute period.

Experimental Design

Immediately following cystoscopy, the blinded physician evaluated as excellent, good, fair or poor the sedative effects produced by the test medication. The assessments included: (1) patient cooperation, (2) muscle relaxation, (3) ease of cystoscopic examination, (4) quality of sedation, (5) control of bladder spasms, (6) control of pain, (7) control of retching and vomiting, and (8) overall tolerance of the procedure. One hour after

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cystoscopy and one day later in a follow-up questionnaire, patients evaluated the sedation during the procedure as excellent, good, fair or poor. In addition, on both occasions, patients were asked whether they would elect to undergo a future cystoscopy the same way, if necessary. One hour after cystoscopy, patients evaluated the procedure as not painful, somewhat painful or very painful and whether they could recall none, some or all of the procedure. One day later in the follow-up questionnaire, patients were also asked whether they could recall clearly, vaguely or not at all events before, during and after cystoscopy.

Recovery from sedation was assessed by the Trieger Test which was completed by the patient before medication (baseline) and at 60 and 120 minutes following the completion of the cystoscopy. Each Trieger Test was evaluated for the number of dots missed and the total deviations (mm) from the dots.

Vital signs were monitored before, during and after cystoscopy. Changes in vital signs greater than 20% from baseline were identified as possible adverse experiences. The severity of the change was categorized as:

mild = a change $\geq$ 20% but $<$ 30% from baseline
moderate = a change $\geq$ 30% but $<$ 50% from baseline
severe = a change $\geq$ 50% from baseline or treatment required

Clinical adverse experiences were further categorized according to the phase of the study, as induction, maintenance (cystoscopy) and recovery. Seven to 14 days following the study, the intravenous injection site was examined for tenderness, redness, and induration.

Results

Deviations from Protocol

No data were reported for the physician's assessment of control of pain for patient of the placebo (midazolam) group. Patient of the placebo (diazepam) group did not answer the questions regarding: quality of sedation and a future procedure done the same way on the 24 hour questionnaire.

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.089 mg/kg of midazolam and 0.089 mg/kg of diazepam. Two midazolam-treated patients and three diazepam-treated patients required maintenance sedation doses to complete the cystoscopy. The mean time required to reach the

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sedative end point was comparable between midazolam and diazepam treatment groups.

Physician's Assessment

The physician's assessments of sedation for midazolam patients were "excellent" for most parameters. The assessments for patients who received diazepam, and both placebos ranged from "poor" to "excellent". Patients who received midazolam were evaluated as significantly better than placebo patients for muscle relaxation, ease of cystoscopic examination, quality of sedation, control of bladder spasms, and control of pain. Midazolam patients were rated significantly better than diazepam patients for quality of sedation, control of pain, control of bladder spasm and control of retching and vomiting. Patients who received placebo had significantly better control of retching and vomiting than did diazepam patients.

Patient's Assessment

One hour after the procedure, midazolam patients rated sedation significantly better than patients who received placebo. On the following day, both midazolam and placebo (diazepam)-treated patients evaluated sedation significantly better than diazepam-treated patients. Midazolam patients experienced significantly less pain associated with the cystoscopy than did placebo (midazolam) and diazepam-treated patients. There were no significant differences between groups for patients who were willing to have a future cystoscopy done the same way.

Trieger Test

Midazolam patients missed significantly more dots on the one hour Trieger Test than did diazepam and placebo treated patients. Midazolam patients also had a significant increase in deviation from the dots when compared with placebo (midazolam) treated patients on the one hour Trieger Test. At two hours there were no significant differences between any of the treatment groups.

Follow-Up Questionnaire for Amnesia

Only 40% of the midazolam patients could recall receiving the local anesthetic. Failure to recall the procedure was induced in most midazolam patients and was extended to two hours in many, since they could not recall the post-treatment Trieger Tests. There was significantly less procedural recall for midazolam than placebo as well as recall of the one hour Trieger Test. There was also significantly less recall of the scope withdrawal in the midazolam group compared with the diazepam group.

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Safety

One diazepam patient and one placebo (midazolam)-treated patient experienced tenderness (burning) at the injection site during administration of the ten drug. Neither of these patients had evidence of irritation at the injection site on the follow-up examination.

Patient\ experienced dizziness 45 minutes after receiving meperidine but prior to the administration of placebo (midazolam). The dizziness, therefore, was remotely related to the administration of placebo (midazolam).

Most changes in vital signs were transient and were not considered clinically significant. No changes were observed during induction of sedation. All changes were classified as mild or moderate.

Summary and Conclusions

This was a randomized, double-blind study. It compared the use of intravenous midazolam with I.V. diazepam and placebo as an adjunct to intramuscular meperidine and local anesthetic administration to provide sedation for cystoscopy. For the physician's and patient's assessments, midazolam-treated patients experienced significantly more sedation than diazepam and placebo (midazolam)-treated patients. Midazolam patients also reported significantly less pain associated with the cystoscopy than did patients in the diazepam and placebo treatment groups. Since the dose of diazepam received by most patients was somewhat low, most diazepam-treated patients probably did not reach the optimal sedation level.

Midazolam patients missed significantly more dots on the one hour Trieger Test than did diazepam and placebo patients and had a significant increase in deviation from the dots when compared with placebo (midazolam) patients. This suggests impairment of psychomotor performance; however, by two hours the results had returned toward the baseline value. Retrograde and autegrade failure of recall was induced in many patients who received midazolam.

Transient fluctuations in vital signs were observed in all treatment groups but were not considered clinically significant. One diazepam and one placebo (midazolam) treated patient experienced burning during the injection of the study drug. There were no reports of irritation at the intravenous injection site on follow-up.

This study showed that I.V. midazolam when used in combination with meperidine and a topical anesthetic agent is as safe as diazepam in inducing sedation for cystoscopy. It appeared to be more effective than diazepam in producing sedation but this may have resulted because of low doses of diazepam.

PHARM REVIEW

2/20/80

Pharmacology and Toxicology Review
of Original NDA 18-163

Amendments of 7/25/79 and 10/2/79

Sponsor: Sandoz Pharmaceuticals
East Hanover, New Jersey 07936

Drug: Restoril (temazepam) Capsules 15 and 30 mg.

Category: Hypnotic

Previous Pharmacology Reviews: Original NDA 12/21/78

Pertinent Correspondence:

The reply to our letter of 1/10/80 concerning conformance to GLPR of the 2 year rat study) and the 1 year dog study) as well as clarification of certain aspects of these studies as per our telephone conversation with Sandoz on 2/4/80 were satisfactory (Submissions dated 2/4/80 and 2/8/80, respectively.)

Preclinical Studies:

1. Two year oral toxicity/carcinogenicity study in rats.

(Amendment 10/2/79).

2. One-year oral toxicity in dogs.

(Amendment 7/25/79).

A. Rat (Charles River CD; weanling.

90 M + 90 F at 0, 10, 40, 160 mg/kg/day in the diet for 104 weeks. Interim sacrifice of 10 M + 10 F at 26 and 52 weeks. Terminal sacrifice at 104 weeks.

1. Observed Effects: No drug-related behavioral effects

2. Mortality: 29 C, 42 LD, 40 MD, 46 HD M; 28 C, 41 LD, 33 MD, 29 HD (includes animals sacrificed in extremis). Increased mortality in treated M and LD F from about week 85 on.

3. Body Weight/Food Consumption (weekly): Progressive decrease in body weight gain of HD groups of 20-150g (5 to 25% decrease compared to controls) from week 26 to term. Dose-related decrease in mean weight gain in treated female at term.

Decreased food consumption of about 10% for HD rats from wk 53 to term. Sporadic decreases for all other test animals but no greater than about 12% of control consumption.

4. Hematology: (18 hr. fasted blood sample: 5C M&F and 5 HD M&F at 13 weeks; 10/sex/dose at 26, 52, 78, 104 wks.):

Parameters were hematocrit, hemoglobin, erythrocyte, reticulocyte, total and differential leucocyte. No measure of clotting mechanisms.

Leucocytes were decreased in HD M at wks 26, 78, 104 and in HD F at term but values were within the normal range. Relatively higher neutrophils and lower lymphocytes were observed in HD M at wk 78.

5. Clinical Chemistry (schedule as above): Glucose, BUN, SGPT

No dose-related changes.

6. Urinalysis (Schedule as above): Volume, pH, S.G., protein, glucose, ketones, blood, sediment, appearance.

No compound-related effects.

7. Ophthalmic Examination (All surviving rats wks 1, 12, 25, 51, 103):

No dose related effects.

8. Organ Weights: Absolute (20%) and relative increase in mean liver weight of HD M at 6, 12, and 24 mos. sacrifice.

Relative increase (15-30%) in liver weights of HD F at all sacrifice times.

9. Gross Pathology (All spontaneously dying and sacrificed rats):

MALE

	0	LD	MD	HD
	% of tissues examined			

1-12 mo.: no dose-related effects

13-24 mos.:

Kidney

Enlarged	11	9	22	27
Cortical cysts	15	12	23	27

Parathyroid

Enlarged	5	12	16	22

10. Histopathology (C & HD spon. deaths and sacrificed at 6 mo.; all animals dying or sacrificed at other times):

a. Non-neoplastic Lesions (% of tissues examined)

	MALE				FEMALE			
	0	LD	MD	HD	0	LD	MD	HD
1-6 mo:								
LIVER								
Cytoplasmic Vac.	20		27	100	30	9	18	84
Hypertrophy				77				25
KIDNEY								
Nephrosis	10		9	46	20			8
7-12 mo:								
LIVER								
Cytoplasmic Vac.			18	75				8
Lipid (ORO)	28	6	54	83				
13-24 mo:								
LIVER								
Cytoplasmic Vac.	26	20	18	26 more severe	18	15	15	23 more severe
Lipid	97	94	94	94	99	94	91	97
KIDNEY								
Ep. Hyperplasia	10	8	9	22	13	29	28	29
Cortical Cyst	17	17	24	32	1	4	4	3
PARATHYROID¹								
Hyperplasia	11	23	20	29	4	3		5
ESOPHAGUS								
Dilation				6				15

¹ About 20-50% of the parathyroid tissue from each group was missing or unsuitable for histology.

b. Neoplastic lesions: Results are comparable in control and treated animals regarding types of tumors and incidence of each. The great majority of tumors were observed in animals dying or sacrificed during 13-24 months. No clear trend is noted in the total number of tumors in spontaneously dying versus terminally sacrificed rats. The incidence of tumors in various organs generally compares well with the reported spontaneous incidence of tumors in 24 mo. old C R CD rats (NCI data: J. Nat'l. Can. Inst. (1979) 62:952) but exceptions are increased rates of liver tumors and thyroid tumors in this experiment.

Liver and Thyroid Tumors (%)

	MALE				FEMALE			
	0	LD	MD	HD	0	LD	MD	HD
LIVER								
Carcinoma	11	10	6	11	14	4	11	9
NCI tumors	1.1				2.2			
THYROID								
Carcinoma ¹	9	1	1	10	6	6	6	1
Adenoma	6	4	7	2	2	3	10	4
NCI tumors	3.8				0			

¹ A statistically significant greater number of thyroid carcinomas were found in HD M dying before term compared to control rats dying during this time. At term sacrifice control rats exhibited a somewhat higher incidence of thyroid carcinoma than HD rats.

Summary of Total Tumors

	MALE				FEMALE			
	0	LD	MD	HD	0	LD	MD	HD
No. Benign tumors	89	54	69	61	121 ¹	122	117	72 ¹
No. of rats affected (%)	60 (66)	42 (53)	45 (56)	44 (49)	63 (70)	65 (81)	61 (76)	46 (51)
No. Malignant tumors	29	22	19	32	27	21	29	17
No. of rats affected (%)	24 (27)	21 (26)	18 (18)	29 (32)	27 (30)	15 (19)	26 (33)	15 (17)

¹ High incidence in F due to mammary tumors. Relative low incidence in HD F due to low no. of mammary tumors in this group.

B. Dog (Beagle, 5 mo. old. Marshall Res. Animals, Inc., North Rose, NY):

4 M & 4 F at 0, 15, 45, 135 mg/kg/day in 2 capsules daily for 52 wks. Sacrifice at wk. 53.

1. Observed Effects: Dose-related uncoordination throughout treatment period. Severity of uncoordination appears to decrease in HD and increase in LD at 6 mo. Lesser incidences of

2. Mortality: 1 M & 1 F HD dogs at wks. 23 and 37, resp. M exhibited convulsions the day before death and blood was found at the top of the brain at autopsy. Death was attributed to chronic enteritis secondary to viral infection (M) and to acute hemorrhage of ileal ulcer secondary to peracute viral infection (F). Marked decreased food consumption was noted in F the week before death.
3. Body Weight/Food Consumption (0 & weekly): HD M initially weighed on average about 1 kg more than controls. After treatment HD M failed to gain as much weight as controls up to about wk 11; thereafter, weight gain was 1-2 kg greater than controls.

MD and HD F gained more weight relative to C and LD dogs from about wk 15 on.

Food consumption was uniformly high in HD dogs compared to greater fluctuations in controls.
4. Hematology (18 hr. fasted sample at 0, 4, 8, 13, 26, 52 wks): Hematocrit, Hb, RBC, Leucocyte-total and diff., Ret., Platelet, Clotting time, Ery. sed. rate.

Increased erythrocyte sedimentation rate in 3/4 HD M and 1/4 HD F at various times during the study.
5. Clinical Chemistry (Schedule as above): SGOT, SGPT, SAP, BUN, Glucose, PO₄, Na, K, CL, total protein and electrophoresis.

No drug-related effects.
6. Urinalysis (Schedule as above): Glucose, protein, ketones, bilirubin, blood, sed., appearance, S.G., pH.

No drug-related effects.
7. Ophthalmological Exam (0, 13, 23, 51 wks):

No drug related effects.
8. ECG (0, 12, 25, 51 wks):

Normal
9. Organ Weights: Absolute and relative increase in liver weight in 2 HD M and abs. increase liver weight in 2 HD F.
10. Gross Pathology: White frothy material (not identified) was observed in the stomach of 0/4 C, 4/4 LD, 3/4 MD, 3/3 HD M and 0/4 C, 4/4 LD, 4/4 MD and 3/3 HD F dogs.

11. Histopathology: No drug-related changes. Various lymphoid hyperplasias and pneumonia were noted in control and treated dogs. One MD F had a primary fibrosarcoma of the hindfoot with metastases to the spleen and lung.

Summary and Evaluation:

In their letter of 10/1/79, Sandoz referred to several recent submissions that addressed the deficiencies of the original NDA and requested that the file on temazepam be reopened. The FDA nonapprovable notice had been based in part on preclinical labeling deficiencies as well as on the questionable validity of the IBT dog toxicity study. We also requested validation of the IBT dog study by the Division of Scientific Investigations (HFD-180) and the completion of a 2-year rat study. Following their investigation, HFD-180 recommended that the IBT dog study not be accepted in support of the safety of temazepam (memo dated 10/26/79). The firm has withdrawn both the dog study and the IBT 2-year rat study and has submitted another 1 year dog study conducted by [redacted] and the final report of a 2-year rat toxicity/carcinogenicity study conducted by IRDC which are reviewed here.

Two Year Rat Study. No pharmacological or behavioral signs were observed among any of the treated animals. Mortality in each group of treated males and in low dose females was about 1.5 times the mortality in control rats with most deaths occurring after 20 months. The incidence of parathyroid hyperplasia was increased relative to controls in treated males dying during 13-24 months without dose relationship. Parathyroid hyperplasia can result from chronic nephritis and indeed moderate to severe nephritis was noted in all cases. That nephritis was not secondary to parathyroid hyperplasia is indicated by the absence of a corresponding incidence of renal calculi in these rats. The incidence and severity of nephritis appeared slightly greater with dose relationship in treated male rats dying before term sacrifice but these parameters were comparable in control and test males sacrificed at term. On the other hand rats receiving the high dose of 160 mg/kg exhibited several drug-induced toxicities. HD male and female rats showed progressive decreases in body weight gain of 5-25% from week 26 on and about 10% decreased food consumption compared to controls. Absolute and relative liver weights were increased in HD M and relative liver weights were increased in HD F. Hepatocellular hypertrophy was reported in most HD M and some HD F sacrificed at 6 months but not at later sacrifice times. Centriobular cytoplasmic vacuolation consisting of accumulated lipid material was observed in HD M and F at 6 and 12 months. At later necropsy times hepatic vacuolation was observed in comparable numbers of control and treated rats but HD animals were more severely affected. Kidney nephrosis was observed in a high percentage of HD M at 6 months and there was an increased incidence of kidney epithelial hyperplasia and cortical cysts in HD M autopsied during 13-24 months. All other kidney pathology was of similar incidence at term in control and HD rats. Esophageal distention occurred in a small number of HD M and F but not in controls or rats receiving lower doses of temazepam.

There was no evidence of drug-related carcinogenicity. In general, the control groups had a higher proportion of tumors compared to treated groups and there was no statistical increase in the number of specific benign or malignant tumors in treated rats. It is noted, however, that liver carcinomas and thyroid tumors while not differing in incidence in control and test rats occurred in much higher frequency in this experiment compared to NCI published control values for this strain. Liver cell adenomas and peliosis hepatitis, observed in mice after treatment with oxazepam (Rec. Comm. Chem. Path. Pharm. (1974) 8:481) a principal metabolite of temazepam, have not been reported in this study nor in an earlier 2 year mouse study with temazepam (, Pharmacologist review 4/5/76). Liver tissue slides from control and HD temazepam-treated rats have been submitted (10/18/79) and our comparative review of these and liver slides from other studies with benzodiazepine drugs may help to sort out various liver pathology induced by this class of drug. The distribution of thyroid tumors in this study was also somewhat unusual. Of male rats dying spontaneously or killed in extremis between 1 year and terminal sacrifice 0/25 C, 1/39 LD, 3/39 MD and 8/41 HD rats exhibited thyroid tumors. This positive dose-response, primarily due to thyroid carcinoma, is statistically significant. The corresponding incidence for term sacrificed M rats was 12/41, 4/28, 4/30, and 3/24 for C, LD, MD and HD rats, respectively. In this case the differences among groups is reported not statistically significant. Because some of the decedant rats with tumors were near the age of term sacrificed rats, it was decided after consultation with Dr. Gerry Senturia (HFD-232) to determine whether the statistical analysis were biased by heterogeneous mortality in the different groups. The Peto calculation for comparing incidental tumors (Brit. J. Cancer (1974) 29:101) was employed after first dividing all necropsies from 12 month sacrifice to term into 10 periods of 5 weeks each and listing the number of tumors found at each period. It was found that the incidence of total tumors or thyroid carcinomas was not statistically different in control and HD M whereas the incidence of thyroid carcinoma was decreased in LD and MD M compared to control and HD M rats.

Conclusion: The data indicate that temazepam doses of 40 mg/kg/day are well-tolerated by the rat when administered for up to 20 months. Thereafter, mortality was higher relative to controls in M rats receiving 10, 40, and 160 mg/kg and in F rats receiving 10 mg/kg. A causal relationship between drug treatment and mortality is, however, doubtful due to the lack of dose response and absence of consistent toxicity in the lower dosage groups. Continuous treatment for up to 2 years did not increase the incidence of total or specific tumors above the level seen in controls.

Additional Notes:

1. The Pharmacologist Review (12/21/78) of the interim report of this study noted that plasma concentrations of temazepam in female rats were substantially higher than levels in males and

recommended that this be further explored in humans and dosage adjusted, if necessary, for men and women. While it was found that F rats had proportionally higher mean blood levels than males at 6, 12, and 24 month sacrifice any significance seems questionable because the wide range of blood levels with large overlap between groups was probably due to ad libitum feeding on drug-diet prior to blood sampling. This experiment at best allows only a rough estimate of absorption by indicating a positive relationship of plasma levels to dosage.

2. The previous Pharmacologist's Review also asked for clarification of the 2 different expiration dates given for 2 batches of the same lot of temazepam (memo; telephone conversation with Sandoz on 2/4/80). The firm explained that the expiration date on the first batch was based on stability data developed up to that time but further analysis showed temazepam to be stable for a longer period of time and a second expiration date was then applied. The firm has submitted complete diet and compound analysis data showing stability and purity of drug used in the study (Amendment of 10/2/79 and 2/8/80).

One year dog study. Dose-related uncoordination was observed with severity increasing in LD dogs and decreasing in HD dogs at six months. Sporadic incidences of lethargy, polydipsia, emesis were noted mainly in HD dogs. One HD male died during week 23 after exhibiting convulsions the day before. Various hyperplastic lymphoid tissue and widespread inflammation of the intestines was found at autopsy. One HD female also died during week 37. Hemorrhages and ulcers were noted throughout the GI tract and death was attributed to acute hemorrhage of the ileum. The authors state that the intestinal pathology was a severe manifestation secondary to viral infection that appeared to be endemic in the colony. This analysis is supported by observations of increased erythrocyte sedimentation rates at various times in 1 LD, 1 MD, 3 HD M and 1C, 1 HD F; enlarged lymph nodes in 1C, 1 LD, 1 MD, 2 HD M and 1C, 1 HD F; hyperplastic lymphoid tissue in 1 LD, 1 HD M and 1C, 3 LD, 2 HD F; and pneumonia in 1C, 1 LD, 2 HD M and 1 C, 1 LD, 1 MD, 1 HD F. The somewhat greater susceptibility of HD animals to infection may be related to stress imposed by drug-induced psychoneurological effects in these animals.

Conclusion:

These data indicate dose-related uncoordination at all dosage tested but no drug-related organ pathology at doses up to 135 mg/kg.

Additional Notes:

1. We requested a further explanation of the findings of white frothy material in the stomach and of tacky mucus material in the intestine of test dogs (telephone memo dated 2/4/80). Dr. John H. Rust, pathologist in the study, replied that quantitation of the stomach material was subjective but it was

his considered opinion that it was a manifestation of long fasting and not drug treatment. He has observed the same effect in dogs in a variety of other studies. At one time a coworker of his attempted to identify this material and found it consistent with pancreatic secretion. The firm provided data in graphic format showing the positive relationship between fasting time and the appearance of stomach froth and/or mucus in the intestine. They did not send the requested individual fasting and sacrifice times for each dog. However, in view of Dr. Rust's experience, the absence of stomach froth in dogs dying during the study, and the lack of dose-related gastric lesions it appears reasonable to conclude that these findings are not directly a result of temazepam treatment.

Recommendations:

1. The preclinical requirements for this NDA are complete and the NDA is approvable pending satisfactory revision of the package insert.
2. The package insert submitted on 6/15/79 should be revised to conform to current labeling guidelines. Temazepam should be placed in Pregnancy Category D. Under the appropriate warning section the positive evidence of human fetal risk with diazepam should be mentioned and the results given of temazepam reproduction and teratology studies in animals. (Note: the description of reproduction effects is accurate in the labeling submitted 6/15/79). Under "Precautions" (3) Laboratory tests: recommendations should be given for monitoring liver and kidney function in patients on long-term temazepam use. Under (5) Carcinogenesis, mutagenesis, impairment of fertility: results of long term studies in animals to evaluate carcinogenesis should be given.
3. Summary Basis of Approval
 - A. Temazepam is a benzodiazepine derivative that differs structurally from diazepam only by a hydroxyl at the 5-position of the diazepine ring and from oxazepam by a methyl group at the 1-position of the diazepine ring.
 - B. Sandoz has submitted toxicity/carcinogenicity studies in mice at 10, 80 and 160 mg/kg/day and in rats at 10, 40, 160 mg/kg/day (equivalent to 20, 80, 320 times the recommended human dose) as well as a chronic toxicity study in dogs at 15, 45, and 135 mg/kg/day. Mice receiving the highest dose had increased incidences of hyperplastic liver nodules and telangiectasis compared to controls. Rats ingesting the high dose exhibited hepatocellular hypertrophy with cytoplasmic lipidosis and a somewhat higher incidence and enhanced severity of kidney pathology including epithelial hyperplasia and cortical cysts. Esophageal distention also occurred in some high dose rats. Although mortality was greater relative to controls in all treated males and in

females receiving the low dose, a causal relationship of drug treatment to mortality is doubtful because of the lack of dose response and the absence of consistent toxicity in the lower dosage groups. The incidence of total or specific tumors was not increased in mice or rats after long term temazepam treatment. All dogs receiving temazepam in the 1 year study showed dose-related uncoordination but no consistent toxicity or organ pathology that could be associated with drug treatment. Reproduction studies were conducted in rats and rabbits. In a perinatal-postnatal study (segment III) in rats doses of 60 and 120 mg/kg/day but not 30 mg/kg/day resulted in higher nursing deaths. Teratology studies in rats demonstrated increased fetal resorptions at doses of 30 and 120 mg/kg/day and an increased incidence of rudimentary ribs, which are considered skeletal variants, at doses of 240 mg/kg or higher. In pregnant rabbits doses of 40 mg/kg/day resulted in the increased occurrence of rudimentary 13th ribs. No major fetal malformations were seen in any study that could be attributed to temazepam treatment.

Drug metabolism studies with temazepam in mice, rats, dogs, and man showed that conjugated temazepam and conjugated oxazepam were the two principal urinary metabolites. Studies in absorption and excretion of temazepam in man indicated that the drug is well absorbed through the GI tract. Peak plasma levels were reached with 2-3 hours and declined with biphasic T half values of 0.6 and 9 hours. Similar absorption, time to peak plasma levels and plasma T half life were found in mice, rats and dogs. When temazepam was given to pregnant rats, temazepam and its metabolites were found in the fetus and also detected in the mother's milk. Temazepam showed drug dependence liability in monkeys which at minimum was equal to chlordiazepoxide.

- C. The relevant toxicities in rodents after chronic treatment with high doses of temazepam involve liver changes of hypertrophy, lipidosis, and hyperplasia and kidney pathology including enhanced nephritis, epithelial hyperplasia and cortical cysts. The firm has recommended in the event of repeated temazepam use in patients that liver and kidney function tests be performed and that the usual precautions should be observed in patients with impaired renal or hepatic function (package insert, 6/15/79).
- D. Comment on labeling deferred pending Sandoz revision according to current labeling guidelines.

Ann L. Wilk, Ph. D.
Pharmacologist

cc:
ORIG NDA
HFD-180
HFD-120

HFD-120/VGlocklin
HFD-120/AWilk:dc:3/5/80
DOC 0827A

3/10/80

Toxicology and Pharmacology Review of NDA 18-163

Submission of 2/26/80

Sponsor: Sandoz Pharmaceuticals
East Hanover, New Jersey 07936

Drug: Restoril (temazepam) Capsules

Subject of Review: Package Labeling

Labeling Recommendations:

1. Revise "pregnancy" section to conform to that of other benzodiazepines. That is, delete paragraph given and add: Pregnancy Category D. See Warnings section.

2. Under "Warnings" supply the appropriate clinical information and then add:

"Reproduction studies in animals were performed in rats and rabbits. In a perinatal-postnatal study in rats, oral doses of 60 mg/kg/day resulted in increasing nursing mortality. Teratology studies in rats demonstrated increased fetal resorptions at doses of 30 and 120 mg/kg in one study and increased occurrence of rudimentary ribs, which are considered skeletal variants, in a second study at doses of 240 mg/kg or higher. In rabbits, occasional abnormalities such as exencephaly and fusion or asymmetry of ribs were reported without dose relationship. Although these abnormalities were not found in the concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg or higher, there was an increased incidence of the 13th rib variant when compared to the incidence in concurrent and historical controls."

3. Revise "Overdosage" section. Delete references to preclinical toxicology in the last two paragraphs. It is felt that information on clinical pharmacology may be of more use in treating overdose than any pharmacokinetic data from animals.

4. "Precautions - Laboratory Tests" section: After the recommendation for periodic liver and kidney function tests, it appears appropriate to mention:

"Chronic treatment of mice with high doses of temazepam results in an increased incidence of hyperplastic liver nodules and telangiectasis. Repeated administration of high doses to rats causes liver hypertrophy and lipidosis and increases the incidence of kidney pathology including enhanced nephritis, epithelial hyperplasia, and cortical cysts."

Ann L. Wilk
Ann L. Wilk, Ph.D.
Pharmacologist

cc:
Orig. NDA
HFD-120
HFD-120/AWilk/3-6-80
VGlocklin
JCole
HFD-180
FT/ap/3-10-80
DOC#0975Ap2

HFD 12~

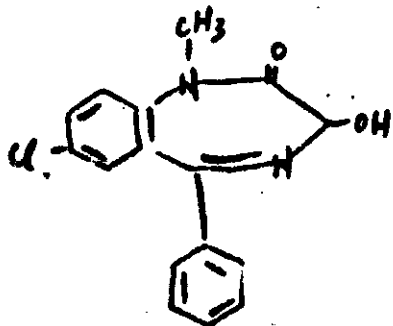
PHARMACOLOGIST'S REVIEW OF NDA 18-
ORIGINAL SUBMISSION 6/21/78
AMENDMENT 11/03/78

SPONSOR:

Sandoz, Inc.
East Hanover, New Jersey 07936

DRUG:

Temazepam; Restoril Capsule; 7-chloro-1,3-dihydro-1-methyl-3-hydroxy-5-phenyl-2H,-1,4-benzodiazepine-2-one.



CATEGORY:

Hypnotic

RELATED DRUG(S):

Oxazepam, Diazepam

FORMULATION:

Capsule 15, 30 mg.

PREVIOUS PHARMACOLOGY REVIEWS:

SCIENTIFIC LITERATURES:

PROPOSED CLINICAL USE:

Hypnotic

RELATED INDs:

ACUTE TOXICITIES (Vol. 1.7.3-1)

		LD50	
		P.O.	i.p.
Mouse	M+F	1963	1050
	M	980	485
Rat	M+F	1823	617
	M	2800	670
Rabbit	M+F	> 2400	
Dog	M+F	> 1600	

RE.

Carlo Erba.

EXPERIMENT

ANIMAL SPECIES	ROUTE ADMINI	DOSE mg/kg	RESULT
Mice CF1			
Rat CFE			
Rabbit New Zealand white			

Acute Toxicity (48-hr observation)

Mice CF1	p.o.	LD50-980 mg/kg.	

Vol. 1.7.1 p.9
Carlo Erba

TABLE 2. - PERCENT OF ANIMALS BEARING NEOPLASMS - TOTAL, BENIGN, MALIGNANT AMONG GROUPS OF MICE FED TEMAZEPAM

ANIMALS BEARING NEOPLASMS	PROJECT T-0400 ^a				PROJECT T-0657 ^b			
	Control	low dose	mid dose	high dose	Control	low dose	mid dose	high dose
Total - %								
Male	39	21*	13*	17*	21	10*	11*	3*
Female	30	31	16	25	9	14	14	7
Benign - %								
Male	10	6	3	11	5	1	1	0
Female	2	4	1	5	3	3	1	3
Malignant - %								
Male	32	16*	11*	8*	20	8*	10*	3*
Female	28	29	15	21	6	11	12	4

^a Data from pp. 124, 125, and 139 and 140 of final study report.

^b Data from pp. 110 and 123 and 124 of final study report.

* Statistically significantly lower than controls.

TABLE 3. PERCENT INCIDENCES OF MICROSCOPIC LIVER LESIONS IN MICE FED TEMAZEPAM

HISTOLOGIC DIAGNOSES		PROJECT T-0400 ^a				PROJECT T-0657 ^b			
		control	low dose	mid dose	high dose	control	low dose	mid dose	high dose
hyperplastic nodule(s)	MALE	2	3	3	10*	1	1	0	4
	FEMALE	0	0	1	6*	0	1	6*	11*
hepatocellular adenoma	MALE	8	4	2	10	4	1	1	0
	FEMALE	0	1	1	4*	0	0	1	1
telangiectasis	MALE	0	0	0	1	0	0	0	0
	FEMALE	2	3	9*	10*	0	1	0	0

^a Data from p.107 and p.138 and Tables B-2, B-5, B-8 and B-11 of final study report.

^b Data from p. 96 and Tables B-2, B-5, B-7 and B-14 of final study report.

* Statistically significantly different from controls.

See inter-office memorandum from Dr. William E. Schutz to
Dr. R. J. Van Ryzin, dated March 22, 1978.

Subject: Project #T-0400: A Statistical Evaluation of the Occurrence
of Telangiectasis Among The Female Mice.

Table 1. NUMBER AND SPLITTING OF LESIONS (L) OF MICROSCOPICALLY DIAGNOSED
LIVER PROLIFERATIVE LESIONS IN NICE FRO TUNAZEPAN

Category	Project T-0400			Project T-0507			Project T-0400 & T-0507 Combined		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose	Control	Low Dose	High Dose
Hypertrophic nodules (n)	2	3	10	1	1	4	1.7	2.3	7.6
	0	0	6	0	1	11	0	.6	8.0
	1	1.5	2	.7	1.4	7.7	.9	4.0	1.7
Hepatocellular nodules	0	4	10	4	1	1	6.2	2.9	1.7
	0	1	1	0	0	1	0	.50	1.2
	4	2.5	1.5	2	.7	1.4	3.2	1.7	1.5
Hypertrophic nodules (n) and hepatocellular nodules	10	7	20	.05	2.0	1.4	7.9	5.3	3.5
	0	1	10	0	1.2	6.9	0	1.2	4.1
	5	4	15	2.0	2.1	8.4	4.1	3.2	3.0

n = nodules and detected with both hypertrophic nodules and hepatocellular nodules

ice carcinogenicity studies (Vol. 1.7.3-1.7.6; T400, T657).

Two mice carcinogenicity studies were presented for reviews (T400 and T657). The first study was involved in the leakage of phosgene gas and the second one was initiated. However, the survival rate was poorer in the second study, so the sponsor presented both studies.

Results:

1. Body weight., lower in the treated groups.
2. Mortality rate., increased in the treated groups.
3. Hepatic changes., increased incidences in hyperplastic nodules, hepatocellular adenomas and telangiectasis. (see tables).
4. The percent of animals bearing neoplasms - Total, benign, malignant did not show any treatment-related effect.

TOXICITY STUDIES:

- 1) Rat (Wistar) 6 week at 0, 60 and 120 mg/kg/day, 10M+10F/dose P.O. gavage. (Vol. 1.7.7-1).
 - a) Significant increase in weight of the liver, both in female and male rats. There was a decrease in the weight of the right and left ovaries.
 - b) Histopathological examination showed two HD rats had cytoplasmic vacuolation around the central view of the lobule of the liver. (could be lipid or carbohydrate thesaurosis).
- 2) Rat (Charles River CD) 6 1/2 to 7 weeks at 0.06, 0.125 and 0.25% diet. (Vol. 1.7.7-19). 10M+10F/group.
 - a) Liver weight increased in the treated groups. Livers of five rats which had received 0.25% and two of which had received 0.125% temazepam displayed cytoplasmic vacuolization around the central vein. There was a tissue necrosis in one of the HD rat.
- 3) Rat (Charles River) 13 week t 0.010, 0.025, 0.1% (eq to 8.7, 22.8 and 90.7 mg/kg) (Vol. 1.7.7-52).
 - a) Actural and liver weight increased in HD male, actual and relative weight of kidney and heat weight in LD and HD males also increased. No histopathological changes were seen to be related to changes.

4) Rat (Wistar) 26 wk. at 0, 60 and 120 mg/kg/day. (Vol. 1.7.8-195). p.o. in 1% carboxyl methylcellulose, 4% tween 80, 9% Benzol. 15M+15F/dose, vehicle control 10M+10F.

a) Liver wt. increased in the treated groups. Testicular wt. of the HD male increased.

b) Histologic examination of the livers showed some venous stasis and occasional atrophy in the treated rats.

5) Rat two-year study by Bio-Test (Vol. 1.7.8-253).

The sponsor disqualified this study and initiated a new study by IRDC.

6) Rat two-year study by IRDC (Vol. 1.7.9-3;T946).

Charles River, in diet at 0, 10, 40 and 160 mg/kg. 90M+90F per dose. Started on March 21, 1977.

a) 6-month interim report.

(1) Treatment-related increase of liver weight was observed. The liver of the HD rats showed trace to moderate hepatic lipidosis. There were also focal to multifocal enlargement (hypertrophy) consisted mainly of an increase in the cytoplasmic mass of the hepatocytes that affected.

(2) Some small focus of cardiac fibrosis and chronic inflammatory cell infiltrates were seen in 5/13 HD males and 1/12 HD females, also they were seen in 2/10 control male and 2/10 control female but none in the LD and MD rats.

(3) Plasma concentration of temazepam in nanogram/ml.

	Control	LD (10)	MD (40)	HD (160)
Male	0	19	58	115
Female	0	31	93	174

The concentration in the females were 50% higher than that of the males under the same dosage treatment. The blood levels were not proportion to the dosage given within the sex.

b) One-year interim report (1.7.9A-5).

(1) Body weights were decreased in HD male (7%) and female (14%).

(2) Liver weights were increased in the treated groups. Microscopically, trace to moderate hepatic lipidosis and hyper-

(2) (continued)

trophy of centrilobular and midzonal liver parenchymal cells were seen in HD rats.

(3) Pancreatic lesions were reported in all groups in males only including control. There were fibrosis of islets of Langerhans. In some cases, large bizarre islets were found associated with intra-insular fibrosis. Some times, islands of acinar tissue or intercalated ducts were found in these large complexes of islet tissue. The sponsor indicated that the incidence and severity were similar throughout the groups including the control and could be the spontaneous lesion in the aging rats.

(4) A total of 15 animals had neoplasm. Three (2M,1F) were in control and one each in LD, MD and HD male with lymphocytic neoplasm. One male in LD with bilateral interstitial tumor. One control male had skin papilloma. Pituitary adenomas were reported in one control female, two LD females and 1 HD female. One control male had thyroid carcinoma and one control male each had thymus fibrosarcoma and thymoma.

(5) Plasma concentration at 12 mo. (1.7.9A-258; DM-2-5/12/78).

	Nanogram/ml			
	Control	LD(10)	MD(40)	HD(160)
Male	0	20	81	165
Female	0	32	115	377

(6) Ophthalmoscopic data was not presented in the submission (1.7.9A-15).

7) Dog 10-week, beagle, oral at 0, 80 and 130 mg/kg. 2M+2F per group. (Vol. 1.7.10-5; by Carlo Erba Inst. Therap. Research). Behavior, body weight, blood chemistry, hematology, urinalysis, micro and macroscopic examinations were performed.

It was concluded from this study that liver toxicity of long-term treatment of temazepam should be further studied.

8) Dog 10-week, pure-bred beagle, o, 80, 127 or 200 mg/kg. p.o. in capsule. 2M+2F/group. (Vol. 1.7.10-109; #011979).

a) Mortality: Two males in HD died at the third wk., one female in MD at 10th week.

- b) Appetite and body weight gain: Lower in HD, not much difference in MD and LD.
- c) Behavior: Somnolence and sedation were observed to varying degrees. Emesis happened in most dogs receiving drug on the first day and diminished gradually. Thereafter, emesis was observed on three isolated occasions and loose stools were observed rarely.
- d) Hematology, blood chemistry and coagulation time. At HD, the prothrombin and coagulation time was prolonged significantly in the first week of treatment, however, these values returned to normal by the sixth month. Serum alkaline phosphatases in the HD was elevated at week 3 and in the LD at wk 10.
- e) Histology: Gall-bladder lesions were seen in 2LD and 1 HD dog. Bilirubin and a small quantity of ketone bodies and occasional hyaline casts with many epithelial cells in the microscopic examination in one HD dog. Moderate acinar atrophy of the prostate and atrophy of the thymus. Two-bone marrow hyperlasia were reported, one in HD and the other in LD dogs. Severe prostate wt. decrease (about 40% of that of control) was reported.

9. 14 weeks oral toxicity study in dogs (Vol. 1.7.10-161; T1-1/21/72). Oral, at 0, 10, 20 and 40 mg/kg/day.

At the doses administered, no sedation, ataxia decreased locomotor activity or any unusual hematology, blood chemistry, ophthalmoscopic and post-mortem findings were reported.

The dosages used in this study were very low.

10. 26 wks oral toxicity study in dogs (Vol. 1.7.12-1; Carlo Erba). Oral in carboxy-methylcellulose, tween 80 and benzyl alcohol solution. Beagles. at 0, 80, 120 mg/kg. Control 3M+3F, LD, HD each has 3M+2F.

a) There were some variations of liver transaminase activity, however, by the end of 6 months, they were returned to normal limits. From the liver weight and histopathology data, it was concluded that tem-pazepam did have some effects on the liver.

b) Some animal in HD had episode of convulsion.

11. One-year chronic oral toxicity study in dogs. (Vol. 1.7.13-1; Biotest) at 0, 5, 20 and 80 mg/kg. control, LD, MD each had 8M+8F, HD had 9M+9F. 3M+3F from each group were sacrificed at 26 wks. p.o. in gelatin capsule. Sandoz has audited the data, the slides from intestines, eyes, mammary glands, livers and kidneys were selected for reexamination.

The pathological findings of the livers were one liver granuloma in LDM and one in MDm., congested liver in one LDM, 3Mdf, and one increased portal connective tissue in MDf. Testicular degenerations were reported in 2 control, 3LD, 1 MD and 2 HD males.

This study is under HFD-180 investigation.

Reproduction studies:

- 1) Effects of temazepam on the gonads of male rats. (Vol. 1.7.14-1; Carlo Erba). Segment I, treated male, single dose level, gavage. Rat Sprague Dowley 10M in control 15M at 30 mg/kg/day 6 days/wk for 75 administration, then mated with two untreated female.

Every parameters in the treated group was comparable to that of control except fertility rate, the control was 70% and the treated group was 36% (impregnated both females) and 30% vs. 64% (impregnated one female). All the males in both groups were fertile (at least pregnant one of the two females). No anomalies was reported.

- 2) Effects on the fertility and reproductive performance of male rats. (Vol.1.7.14-25; T1-3/8/72) Segment I, treated males 10 wks. Hazleton Lab. Sprague-Dawley, Charles River, p.o. in diet, 0, 25, 50, 100 mg/kg., (24M+24F)/group.

Every parameter in the treated groups were comparable to that of the control, including the fertility rate.

- 3) Effects on the fertility and reproductive performance of female rats. (Vol. 1.3.14-137; T2-3/8/72). Segment I. treated females. 21-days pre-mating till sacrifice. Hazleton Lab. 0, 25, 50 and 100 mg/kg. 24F/group. The medication was continued throughout mating and also through weaning of the offspring of these matings. Every parameters in the treated groups were comparable to that of control except the days required for successful mating, and survivals of the offspring.

They were 5.7, 7.7, 8.4 and 8.7 days for control, LD, MD, and HD groups. The survival fate of the neonatals were poorer in the treated groups, and most of the mortality occurred in the first five days (Benzodiazepines cross the placenta and are more toxic to neonatals). These effects are expected in this group of drugs.

- 4) Effect on the organogenesis in rat. (Vol.1.7.14-193; Carlo Erba) At 0, 30, 120 mg/kg. p.o. gavage. (carboxymethyl cellulose) 20F/group, Segment II treated from 6th to 15th day of gestation.

The foetal resorptions were higher in the treated groups. The percentage of dams presenting foetal resorption were 54, 77, and 87 for control, LD, and HD. The resorption in respect of total number of implantations were 5, 12, 12 for control, LD and HD. The percentage of late resorptions were 0, 5 and 3 for control, LD and HD. The percentage of foetus with skeletal abnormalities in respect to stained preparations were 54, 58, and 46 for control, LD and HD. In HD group, 24% of the examined foetus presented increased ossification at the anterior end of some ribs (higher than that of control).

Days 6 to 15 of gestation. From pregnant and non-pregnant rats in HD (840 mg/kg)

Page 8

5) Effect on rats (Vol. 1.7.14-222; T2-2/16/72)

Charles River, Sprague Dawley. p.o. intubation. 20F/group at 0, 120, 240 and 840 mg/kg) died during the treatment. Slightly higher resorption rate in HD (1.4 vs. 0.6 in control) rats. Higher incidences of rudimentary 14th ribs were reported in treated groups. They were 16, 17, 26 and 35% for control, LD, MD, and HD.

6) Effects of perinatal and postnatal administration in rats. (Vol. 1.7.14-270; T1-2/14/72). Charles River Sprague-Dawley, oral via gastric intubation. At 0, 30, 60 and 120 mg/kg. 20F/group from day 15 of gestation through weaning (day 42).

Aside from slight sedation of all dams in HD during the three weeks of medication there was slightly higher mortality in the new born in mid and high-dose groups. No other drug-related effects was presented.

7) Effects on organogenesis in the rabbit. Segment II. (Vol. 1.7.14-300; Carlo Erba). At 0, 5 and 20 mg/kg/day. 10, 25 and 20 dams for control, LD and HD. 6th to 18th day of gestation. Caesarean section 28th day. Mortality: 1, 6, 2 for control, LD and HD. The sponsor claimed it was because of pulmonary infection.

The number of foetuses extracted per dam were 9.9, 7.9 and 6.6 for control, LD and H D. The average live foetuses were 9.1, 7.3 and 6.1. The numbers of inseminations were 11.6, 9.4 and 8.2. Total corpora lutea were 12, 10.4 and 8.3.

Fusion of some vertebrae, ribs and varying length of ribs were observed in HD rabbits. Wrong fusion of sternal centres, imperfect development of upper limbs and scapulae, irregular fissurization of cervical column were reported in LD rabbits. None of these were reported in the control group.

8) Teratogenic potential in the rabbit. Segment II (Vol. 1.7.14-354; T 1-2/16/72). New Zealand white treated from days 6 to 18 of gestation, oral via capsule, at 0, 20, 40 or 80 mg/kg. 15F/group.

The average fetus weights were lower in the treated. They were 39.9, 37.5, 37.6 and 35.2 for control, LD, MD and HD respectively. Resorption rates were 3.1, 3.2, 2.4 and 7.4% for control LD, MD and HD respectively. Dose related increase in the incidence of 13th ribs in the fetuses.

No other anomalies were reported.

EXPERIMENT	ANIMAL SPECIES	ROUTE ADMINI	DOSE mg/kg	RESULT	RE
NS Effects					Vol
1. Irwin's behavior test (72 hr. observation)	Mouse	p.o.		varies Hypnosis, hypothermia	Carlo Erba
	CFI				Vol. 1.7.1-41
	Rat				Carlo Erba
Irwing's behavior tests	CFE	p.o.		varies Hypnosis, hypothermia	Vol. 1.7.1-152
	Dog	p.o.		slight reduction in spontaneous activity	Carlo Erba
	Beagle			hypotonia photophobia (80 mg/kg). slight lowering of heart rate	
2. Rota rod motor co-ordination					Vol. 1.7.1-19
	Mouse				Carlo Erba
	CFI	p.o.	ED50	1.2 mg/kg	Vol. 1.7.1-55
	Rat	p.o.			Carlo Erba
	CFE		ED50	17.6 mg/kg	Vol. 1.7.1-22
3. Antimetrazole effect	Mouse	p.o.	ED50	0.23 mg/kg	Carlo Erba
	CFI				
4. Reinforcement of sleep by barbiturate (Hexobarbital 100 mg/kg i.p.)	Mouse	p.o.	0.125	29% increase in sleeping time	Vol. 1.7.1-26
	CFI		0.250	50 increase in sleeping time	Carlo Erba
			0.500	100 increase in sleeping time	
4a. Reinforcement of sleep caused by a barbiturate (Hexobarbital 30 mg/kg, i.p.)	Rat	p.o.	5	increased sleeping time 28%	Vol. 1.7.1-60
	CFE		10	increased sleeping time 58%	Carlo Erba
			20	increased sleeping time 100%	
5. Reinforcement of subnarcotic doses of ethyl alcohol (2 g/kg i.p.)	Mouse male				Vol. 1.7.1-30
	CFI	p.o.	ED50=2.00	mg/kg	Carlo Erba
6. Anti-Amphetamine activity (10 mg/kg i.p.)	Mouse			Negative	Vol. 1.7.1-34
	CFI			Only at doses over 10 mg/kg, there was A reduction in mortality within 24 hrs.	Carlo Erba
7. Intestinal transit of carbon meal	Mouse			Spasmodic effect at certain doses	Vol. 1.7.1-37
	CFI			Tested	Carlo Erba

EXPERIMENT	ANIMAL SPECIES	ROUTE ADMINI	DOSE mg/kg	RESULT	RE
Spontaneous activity	Rat CFE	p.o.	ED ₅₀ of reduction 17.02 mg/kg		Vol. 1.7.1-47 Carlo Erba
Warner's conditioned avoidance reflexes	Rat	p.o.	From 10 mg/kg. the number of conditioned responses decreases progressively and reaction time lengthen		Vol. 1.7.1-64 Carlo Erba
Operant conditioning (light discrimination pattern)	Rat CFE	p.o.	Lapse of time in response increased No change in correct responses		Vol. 1.7.1-70
Operant conditioning (30 sec. variable interval)	Rat CFE	p.o.	Slightly reduced quality of work.		Vol. 1.7.1-126 Carlo Erba
Operant conditioning (30 sec. variable interval with pre-adversive stimuli)	Rat CFE	p.o.	Showed markedly inhibition of anxiety.		Vol. 1.7.1-140 Carlo Erba
EEG study of the antiepileptic activity	Rabbits		Synchronization o-f EEG possible site of actions: hippocampus, amygdaloid and posterior hypothalamus		Vol. 1.7.1-181 Carlo Erba
CNS profile	mice	p.o.	Antianxiety with marked muscle relaxant properties.		Vol. 1.7.1-200
a) Anti-metrazole		p.o.	ED ₅₀ =0.7 mg/kg		
b) Max. Elect. Shock		p.o.	ED ₅₀ =2.6 mg/kg =0.4 mg/kg, with SKP525-A		
c) Conflict			Attenuated		
Conflict behavior in rat	Rat	p.o.	Attenuated		Vol. 1.7.1-210
Conflict behavior in rat	Rat	p.o.	Attenuated		Vol. 1.7.1-211
Anti-emetic effects against apomorphine	Dog	p.o.	2 No effect		Vol. 1.7.1-212
Muscle relaxing activity	Cats	p.o.	Some effect		Vol. 1.7.1-214

Drug metabolisms:

1. Absorption, blood level, distribution and excretion in the mouse.
(Volume 1.7.2-14; DM-1-7/19/77) $F\text{-value} = \frac{\text{conc./ml. or mg.}}{\text{Dose (mg/kg.)}}$

A) Blood level:

p.o. The drug was detected at first sampling at 0.5 hr.
(80 mg/kg.) The blood levels peaked at 4 hrs. (19.0 ug ef.ml.)
The levels diminished in biphasic manner with half-lives of 2 and 9 hrs.

I.V. (8mg/kg): The initial blood sample obtained at 5 min. showed
3.58 ug eq.(ml.). Then there was a sharp drop in
the first hours. Elimination half-lives were 1
and 8 hours.

B) Tissue distribution:

p.o. After oral administration, the drug levels showed more of a
plateau between 1 and 4 hours. After 4 hrs. all tissues
showed a continuous decline. By 48 hrs. a number of tissues
still contained a significant concentration of the drug, but
no tissue exhibited an F-value greater than 0.03.

I.V. The highest levels of radioactivity found in all tissues was
at 15 minutes. The liver had the highest uptake with an F-
value of 2.570 followed by the kidneys with an F-value of 1.706.
Thereafter, there was a continuous decline with an average ter-
minal half-life of 8 hours found in all tissues. The fat
tissue showed a more rapid elimination of the drug with
shorter half life.

C) Excretion:

P.O.	0-12 hrs.	12-24 hr.
Urine	16.4%	7.9%
Feces	18.1%	31.8%
0-144 hrs. recovery was	97.4%	

V.	0-12 hr.	12-24 hr.
Urine	22.3%	16.3%
Feces	9.38%	29.6%
0-144 hr. recovery was	94.58%	

2. Temazepam excretion following multiple oral doses in the mouse. (Vol. 1.7.2-63; DM1-6/17(77)).

CD1 strain mice were treated for 5 days at 80 mg/kg/day p.o. During the study urine and feces were collected quantitatively from each animal in 24-hr intervals for a period of 8 days.

Results

Urinary excretion:	37.3=1.9%
Fecal excretion :	52.6=1.7%
Cage wash :	1.3=0.1%
Total recovery :	91.2=1.0%
Blood concentration:	26 microgram equivalents of temazepam/ml.

3. Metabolism of diazepam in isolated perfused liver of rat and mouse. (Vol. 1.7.2-73).

Results:

Diazepam → N-Desmethyldiazepam

N-Methyloxazepam → Oxazepam

4. The metabolism of diazepam by liver microsomal enzymes of rats and mice. (Vol. 1.7.2-75).

N-methyloxazepam was metabolized to form oxazepam in vitro by mouse and rat liver microsomes.

5. Species differences in diazepam metabolism. (Vol. 1.7.2-82)

By using liver microsomal preparations, it was found that the mouse liver microsomes metabolize diazepam mostly with the formation of N-demethyldiazepam, while rat liver microsomes form mostly N-methyloxazepam.

N-methyloxazepam is then demethylated by mouse but not rat liver microsomes, while N-demethyldiazepam is hydroxylated to form oxazepam by both species but only at a very low rate in vitro.

6. Quantitation of temazepam and N-desmethyl temazepam in blood and urine of the mouse. (Vol. 1.7.2-87 DM-1-6/30/77) 5th dose 144-hr collections

Urinary dose	% dose
None conjugated temazepam	0.3
Conjugated temazepam	2.6
None conjugated N-desmethyl temazepam	1.5
Conjugated N-desmethyl temazepam	22.6
Total	27.0

7. H^3 Temazepam, absorption, blood level, tissue distribution, and excretion in rats (oral dose). (Vol. 1.7.2-104; p-1-2/22/72).

Single oral dose (10 mg/kg.)

Absorption: 81%

Blood level: peak at 1 hrs.

Tissue levels: peak at 1 hrs. Liver and kidney greater than blood at all time periods.

7. (Continued)

Urinary excretion: 20.8% during 96 hours; 15.5% during 24 hours.
 Fecal excretion: 63.1% during 96 hours; 40.6% during 24 hours.
 Biliary excretion: 59.1% during 24 hours.
 Half-lives: 3 and 12 hours (Blood)

8. H^3 -Temazepam blood level, tissue distribution, excretion and detoxication in the rat (Intracardiac dose) (Vol. 1.7.2-127; DM-1-3/15/74).

Blood level: Highest at 0.5 hr. (first sampling) with biphasic decline.
 Tissue level: Highest conc. at 1 hr. (first sampling). Liver and kidney had the highest concentration at all time periods.
 Urinary excretion: 20.2% (24 hr.) 25.8% (96 hr.)
 Fecal excretion: 35.5% (24 Hr.) 62.3% (96 hrs.)
 The enterohepatic circulation was involved.

Detoxication:

% Blood Activity

Time (hr.)	Temazepam	N-desmethyl-temazepam
0.5	59.4	5.4
1	28.5	9.7
2	11.8	12.3
4	4.8	8.8
6	5.4	6.1

9. H^3 Temazepam excretion following multiple oral dose in the rat (Vol. 1.7.2-66, DM-1-5/23/77). 20 mg/kg/day for 5 days

Urinary excretion: 14.8%
 Fecal excretion: 77.9%
 Total recovery: 92.8%
 Blood conc: 4.9 microgram equivalents of temazepam/ml.

10. H^3 -Temazepam, distribution in pregnant rats, milk, and nursing pups following multiple dosing. (Vol. 1.7.2-177; DM1-6/13/77).

Placental transfer: Temazepam and its metabolites are transferred to the fetuses across the placentas.

Transfer in milk: Temazepam is secreted in the mother's milk.

11. H^3 -Temazepam, determination of the amounts of temazepam and its desmethyl metabolite (oxazepam) in blood, urine and bile and then conjugates in urine and bile of the rat. (Vol. 1.7.2-201; p-1-7/25/72).

Blood:	Unchanged % Radioactivity			
		Temazepam	Oxazepam	
.1 hr.		53	10	
4 hrs.		12	9	
24 hrs.		4	0	
	Unchanged % Dose		Total (+conjugated)	
	Temazepam	Oxazepam	Temazepam	Oxazepam
Urine	1	1	1	1
Bile	1	0	15	1

12. Quantitation of temazepam and N-desmethyl temazepam (oxazepam) in the blood and urine of the rat. (Vol. 1.7.2-216; DMI-6/6/77).

Blood	% Radio activity	Microgram/ml
Nonconjugated temazepam	21.3	1.1
Conjugated temazepam	2.9	0.1
Nonconjugated oxazepam	21.9	1.1
Conjugated oxazepam	<u>0.1</u>	<u>—</u>
Total	46.1	2.3
Urine	% Radioactivity	% Dose
Total	100	14.0
Nonconjugated temazepam	2.5	0.3
Conjugated temazepam	2.4	0.4
Nonconjugated oxazepam	0.6	0.1
Conjugated oxazepam	<u>0.8</u>	<u>0.1</u>
Total	6.3	0.9

13. Temazepam, absorption, blood level, and excretion in the rabbit. (Vol. 1.7.2-237; P-1-10/1/71). Single oral dose 50 mg/kg.

Absorption:	90%
Blood level:	Low, peak between 2 and 4 hrs. F=0.09
Urinary excretion:	90.6% at 96 hrs.
Faecal excretion:	6.2% at 96 hrs.
Half-life:	5 hrs. (blood).

14. H^3 -temazepam, distribution in pregnant rabbits during multiple dosing (Vol. 1.7.2-242; DM-1-6/20/77).

At the steady state concentration of radioactivity in the amniotic fluid and fetuses was low and amounted to about 1/6 the concentration of radioactivity in maternal blood. The placentas contained about 2-3 times the level of radioactivity of the fetuses and amniotic fluid.

15. H^3 -temazepam, absorption, blood level, and excretion in the dog, single oral dose (10 mg/kg.; Vol. 1.7.2-257; P-1-2/11/72).

Absorption:	60%
Blood level:	peak at 2 hrs. $F=0.435$
Urinary excretion:	41.4% (24 hrs.) 54.1% (96 hrs.)
Fecal excretion:	18.2% (24 hrs.) 29.1% (96 hrs.)
Half-lives	2 and 15 hours. (Blood).

16. H^3 -temazepam, blood level, excretion, and detoxication in the dog, single i.v. dose (5mg/kg.; Vol. 1.7.2-269; DMI-11/13/73).

Blood level:	Highest F-Value=0.781 at 0.5 hours. Biphasic decline to $F=0.025$ at 12 hrs.
Urinary excretion:	38.6% (12 hrs.) 52.2% (96 hrs.)
Fecal excretion:	28.2% (12 hrs.) 38.5% (96 hrs.)
Detoxication:	48 hrs. Total 42.7 dose %
	Temazepam 2.6
	N-desmethyl temazepam 1.7
	Conjugated temazepam 28.5
	Conjugated N-desmethyl temazepam 9.9

17. H^3 -temazepam; excretion following multiple oral doses in the dog. (Vol. 1.7.2-289; DMI-5/25/77). 8 days at 20 mg/kg/day.

Urinary excretion:	37.4%
Fecal excretion:	56.8%
Cage wash:	0.6%
Total recovery:	94.8%

Blood conc.: 9.3 microgram equivalent of temazepam/ml.

18. Metabolism of diazepam in vitro. (Vol. 1.7.2-300).

Dog and rat liver microsomes.
Diazepam --- Temazepam --- Oxazepam

19. Temazepam, determination of the amounts of unchanged temazepam and its demethyl derivative (oxazepam) in blood and urine, and their conjugates, in the urine of the dog (Vol. 1.7.2-307; p-2-7/25/72).

None conjugated (% radioactivity)

Blood	Temazepam	Oxazepam
1 hr.	3	4
	1	3

19. (continued)

Urine	Non Conjugated (% radioactivity)		Total	
	Temazepam	Oxazepam	Temazepam	Oxazepam
	1	1	23	19

20. Quantitation of temazepam and N-desmethyl temazepam (oxazepam) in the blood and urine of the dog. (Vol. 1.7.2-321; DM1-6/23/77).

Blood	% blood radioactivity	Microgram/ml.
Non-conjugated temazepam	1.1	0.1
Conjugated temazepam	58.9	5.5
Non-conjugated oxazepam	16.1	1.5
Conjugated oxazepam	<u>20.1</u>	<u>1.9</u>
Total	96.2	9.0

Urinary	% radioactivity	% dose
Total radioactivity (0-144 hr.)	100	42.7
Non-conjugated temazepam	8.6	3.6
Conjugated temazepam	35.1	14.9
Non-conjugated oxazepam	8.6	3.7
Conjugated oxazepam	<u>36.9</u>	<u>15.8</u>
Total	89.2	38.0

21. Metabolism of diazepam and its metabolites by guinea pig liver microsomes. (Vol. 1.7.2.-347).

Diazepam was metabolized in different manner in comparison to that of mice and rats. In vitro, N-desmethyldiazepam is slightly hydroxylated by rats and mice but not by guinea pigs while N-methyloxazepam is demethylated by mice and guinea pigs but not by rats. Oxazepam is not further metabolized by liver microsomes in vitro by mice, rats and guinea pigs.

22. Metabolism of diazepam metabolites in guinea pigs. (Vol. 1.7.2-350).

Demethylated metabolites of diazepam is not readily hydroxylated and that N-methyloxazepam is readily demethylated.

23. Plasma concentrations in the monkey of six related benzodiazepines after intraperitoneal injection. (Vol. 1.7.2.-354).

Half lives for temazepam is 0.60 and 4.56 hrs.

24. A versatile method for the in vitro perfusion of isolated organs of rats and mice with particular reference to liver. (Vol. 1.7.2-356).

25. A method for gas chromatographic determination of benzodiazepines. (Vol. 1.7.2-373).

26. Determination of medazepam, diazepam and their major biotransformation products in blood and urine by electron capture gas-liquid chromatography. (Vol. 1.7.2-376).

EVALUATION:

1. Temazepam is a precursor of oxazepam (after N-demethylation). It is proposed for marketing as night time hypnotic.
2. The sponsor had submitted the following chronic toxicity and reproduction studies for safety review.

Mice: two 18-month carcinogenicity studies. (increased incidences in hepatic nodules, hepatocellular adenomas and telangiectasis).

Rat: 6-week, 6 1/2-week, 13-week, 26-week, 2-year (by IBT), and 2-year (by IRDC, 1 year interim,) studies.

General toxicities were treatment-related liver weight increase. Pancreatic lesions in all groups (fibrosis of islets of Langerhans) were reported by IRDC at the 1-year interim report. The sponsor indicated that the incidence and severity were similar throughout the groups including the control so that it might not be drug-related.

Dogs: 10-week, 10-week, 14-week, 26-week and 1-year (IBT) studies were presented.

General toxicity was seen in the liver. Some animals in HD treated for 26 weeks had episodes of convulsions. The one-year study showed one liver granuloma in LDm and one in MDm; congested liver in on LDm, 3MDF and one increased portal connective tissue in MDF. The IBT 1-year dog study is under HFD-180 investigation.

Reproduction Studies:

Segment I. Rat (treated male), Rat (treated male), Rat (treated female)

Segment II. Rat, Rat, Rabbit, Rabbit

Segment III. Rat

There were slightly increased resorption rate in the treated groups, lower foetus weight and increased super numerous ribs. Some fused or imperfect developed or irregular fissurization cervical column were reported, however, no dose relation was seen.

3. A very comprehensive drug metabolism studies were performed.
4. No drug-depending study was submitted in this original submission, however, there was an amendment submitted subsequent to our request was reviewed by the Drug Abuse Staff.

RECOMMENDATION:

1. In animal study, the plasma concentration of temazepam in female is 40 to 130% higher than that of the male after multiple medication* (no similar data was available in other benzodiazepines). Whether this phenomenon exist in humans should be explored and if necessary the clinical dose in man and woman should be distinguished.

* plasma concentration in rats nanogram/ml

Dose	Control	10 mg/kg/day	40 mg/kg/day	160 mg/kg/day
Male	0	20	81	165
Female	0	32	115	377
F/M		1.6	1.42	2.29

(Vol. 1.7.9A-258)

2. Package Insert:

- The paragraph under "USAGE IN PREGNANCY" should be deleted, and in its place, a standard benzodiazepine pregnancy warning should be placed.
- The sponsor should submit the final report of the IRDC rat study as soon as possible, and the discrepancies of expiration date for temazepam. Lot # C-11764 has to be explained. (Expiration date on p. 9 of Vol. 1.7.9 was 1/78, on p. 11 of Vol. 1.7.9A was 4/79).
- The approval of this NDA is pending on the results of the investigation of HFD-180 on the 1 year IBT dog study. The final report of the 2-year rat study on-going at the IRDC *can be submitted conditional to approval of this NDA.*

Y. Sheu
 Y. Sheu, Ph.D.
 Pharmacologist

cc:

Orig.
 HFD-120
 HFD-120/YSheu/1/24/79
 VGlocklin *1-31-79*
 HFD-180
 FT:mf:1/24/79

CHEM. REVIEW

JAN 22 1985

CHEMIST'S REVIEW (If necessary, continue any item on 8" x 10 1/2" paper. Key continuation to item by number.)		1. ORGANIZATION HFN-120	2. NDA NUMBER 1R-163
3. NAME AND ADDRESS OF APPLICANT (City and State) Sandoz, Inc. Route 10 E. Hanover, N.J. 07936		4. AP NUMBER	
6. NAME OF DRUG Restoril	7. NONPROPRIETARY NAME Temazepam	5. SUPPLEMENT (S) NUMBER(S) S-014	5. SUPPLEMENT (S) DATE(S) 12-18-84
8. SUPPLEMENT(S) PROVIDES FOR: Control changes		9. AMENDMENTS AND OTHER (Reports, etc.) DATES	
10. PHARMACOLOGICAL CATEGORY Hypnotic	11. HOW DISPENSED ☒ RX ☐ OTC	12. RELATED IND/NDA/DMF(S)	
13. DOSAGE FORM (S) Capsules	14. POTENCY (ies)		
15. CHEMICAL NAME AND STRUCTURE		16. RECORDS AND REPORTS	
		CURRENT ☐ YES ☐ NO	
		REVIEWED ☐ YES ☐ NO	
17. COMMENTS Replacement of I.R. identification test			
18. CONCLUSIONS AND RECOMMENDATIONS Review waiting for recommendations			
19. REVIEWER			
NAME V. Iliev	SIGNATURE <i>V. Iliev</i>	DATE COMPLETED 1-15-85	
DISTRIBUTION ☐ ORIGINAL JACKET ☐ REVIEWER ☐ DIVISION FILE			

F/T:GD/1-17-85

HFN-120 HFN-120/V. Iliev/R. Shultz

NYK-DO

CHEMIST'S REVIEW (If necessary, continue any item on 8" x 10 1/2" paper. Key continuation to item by number.)		1. ORGANIZATION HFN-120		2. NDA NUMBER 18-163 /S-013	
3. NAME AND ADDRESS OF APPLICANT (City and State) Sandoz, Inc. East Hanover, NJ 07936				4. AP NUMBER	
6. NAME OF DRUG Restoril		7. NONPROPRIETARY NAME temazepam		5. SUPPLEMENT (S)	
				NUMBER(S) S-013	
				DATE(S) 10/30/84	
8. SUPPLEMENT(S) PROVIDES FOR: for the use of alternate PVC blister material				9. AMENDMENTS AND OTHER (Reports, etc.) DATES	
10. PHARMACOLOGICAL CATEGORY Hypnotic		11. HOW DISPENSED ☒ RX ☐ OTC		12. RELATED IND/NDA/DMF(S) 	
13. DOSAGE FORM (S) Capsules		14. POTENCY (see)			
15. CHEMICAL NAME AND STRUCTURE				16. RECORDS AND REPORTS	
				CURRENT ☐ YES ☐ NO	
				REVIEWED ☐ YES ☐ NO	
17. COMMENTS Alternate blister material US 3002 Two years expiration date to be maintained Commitment for stability					
18. CONCLUSIONS AND RECOMMENDATIONS Approval recommended					
19. REVIEWER					
NAME Viliev		SIGNATURE <i>V. Viliev</i>		DATE COMPLETED 11/13/84	
DISTRIBUTION ☐ ORIGINAL JACKET ☐ REVIEWER ☐ DIVISION FILE					

NYK-DO HFN-120 RShultz init 11/13/84

CHEMICAL REVIEW (If necessary, continue on 8 1/2" x 11" paper. Key continuation to item by number.)		1. ORGANIZATION HFN-	2. NDA NUMBER 18-163
3. NAME AND ADDRESS OF APPLICANT (City and State) Sandoz, Inc. E. Hanover, NJ 07936		4. AP NUMBER	
6. NAME OF DRUG Restoril		7. NONPROPRIETARY NAME temazepam	5. SUPPLEMENT (S) NUMBER(S) DATE(S) 5-012 9/27/84
8. SUPPLEMENT(S) PROVIDES FOR: Alternate assay method		9. AMENDMENTS AND OTHER (Reports, etc.) DATES	
10. PHARMACOLOGICAL CATEGORY hypnotic	11. HOW DISPENSED ☒ RX ☐ OTC	12. RELATED IND/NDA/DMPS	
13. DOSAGE FORM (S) capsules	14. POTENCY (mg)	15. RECORDS AND REPORTS CURRENT ☐ YES ☐ NO ☐ YES ☐ NO	
16. CHEMICAL NAME AND STRUCTURE		17. COMMENTS alternate HPLC method sample of validation request 10/11/84	
18. CONCLUSIONS AND RECOMMENDATIONS permitted recommendation			
19. REVIEWER NAME		SIGNATURE <i>V. Die</i>	DATE COMPLETED
☐ DISTRIBUTION	☐ ORIGINAL JACKET	☐ REVIEWER	☐ DIVISION FILE

cc: NDA/orig.
 877-120
 877-120/Villiev
 r/d endorsed by
 Fleber 10/15/84
 type final 11/3/84:nah;

SEP 2 1983

Orig. NDA 18-163/S009, NDA 18-163/014, HFN 120/Villev/5/20/83, RD/Int:RShttz/5/20/83, FT/AWK/5/20/83

CHEMIST'S REVIEW <i>(If necessary, continue any item on 8 1/2" x 10 1/2" paper. Key continuation to item by number.)</i>		1. ORGANIZATION HEN 120		2. NDA NUMBER 18-163	
3. NAME AND ADDRESS OF APPLICANT (City and State) Sandoz Inc. East Hanover, New Jersey 07936				4. AP NUMBER	
6. NAME OF DRUG Restoril		7. NONPROPRIETARY NAME temazepam		5. SUPPLEMENT (S)	
8. SUPPLEMENT(S) PROVIDES FOR: New dosage form				NUMBER(S) S-009	
				DATE(S) 5-16-83	
10. PHARMACOLOGICAL CATEGORY Hypnotic		11. HOW DISPENSED ☒ RX ☐ OTC		9. AMENDMENTS AND OTHER (Reports, etc.) DATES	
12. DOSAGE FORM (S) Tablets		14. POTENCY (See)		13. RELATED IND/NDA/OMP(S)	
15. CHEMICAL NAME AND STRUCTURE				16. RECORDS AND REPORTS	
				CURRENT ☐ YES ☐ NO	
				REVIEWED ☐ YES ☐ NO	
17. COMMENTS 15 mg and 30 mg Tablets					
18. CONCLUSIONS AND RECOMMENDATIONS Approvable pending satisfactory validation Statistician to evaluate statistical data for stability data					
19. NAME V Iliev		REVIEWER SIGNATURE <i>V Iliev</i>		DATE COMPLETED 5/25/83	
DISTRIBUTION ☐ ORIGINAL JACKET ☐ REVIEWER ☐ DIVISION FILE					

April 9, 1983

Chemist Review of NDA 18-163
Period Report No 6 Dated March 30, 1983

Applicant: Sandoz Pharmaceuticals
East Hanover, NJ 07930

Name of Drug: Restoril (temazepam) Capsules

Indication: Hypnotic

Comments: Raw controls of raw material conform to USP. 1
8 Months stability data are satisfactory (degradation products)
HPLC.

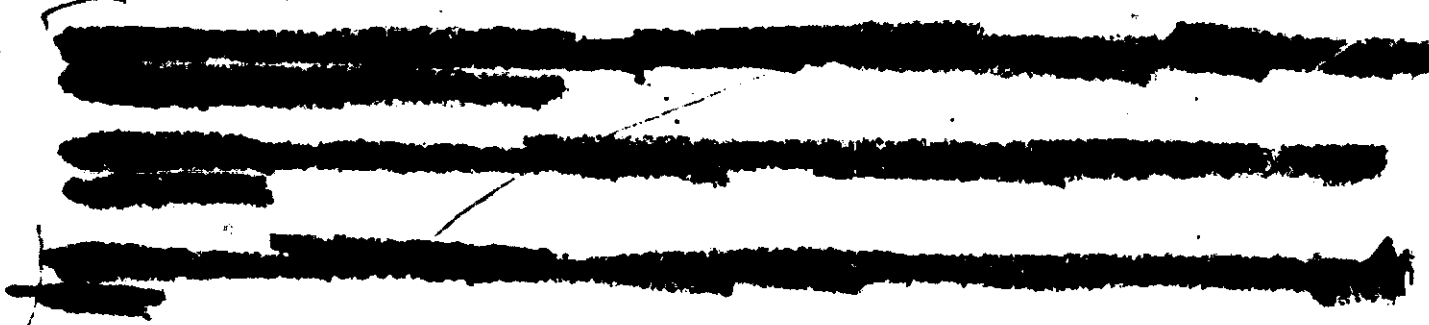
Current labeling is technically satisfactory.

Recommendation: No action indicated.

V. Iliev
V. Iliev
Reviewing Chemist

cc:
Orig NDA
HFN-120 ✓
HFN-120/Viliev/4/19/83
HFN-120/RShultz/4/19/83
cpb/4/20/83/58068

25 1032

CHEMICAL REVIEW (If necessary, continue on 8" x 10" paper. See continuation to (100) by number.)		1. ORGANIZATION HFN-120	2. NDA NUMBER 18-163
3. NAME AND ADDRESS OF APPLICANT (City and State) Sandoz, Inc. Route 10, East Hanover, N.J. 07936		4. AP NUMBER	
6. NAME OF DRUG Restoril		7. NONPROPRIETARY NAME Temazepam	5. SUPPLEMENT (S) NUMBER(S) DATE(S) S-007 9/16/82
8. SUPPLEMENT(S) PROVIDES FOR: — Alternate site for production of temazepam.		9. AMENDMENTS AND OTHER (Reports, etc.) DATES	
10. PHARMACOLOGICAL CATEGORY hypnotic	11. HOW DISPENSED ☒ RX ☐ OTC		12. RELATED IND/NDA/CMFIS
13. DOSAGE FORM (S) capsules	14. POTENCY (10%)		16. RECORDS AND REPORTS CURRENT ☐ YES ☐ NO REVIEWED ☐ YES ☐ NO
15. CHEMICAL NAME AND STRUCTURE		17. COMMENTS	
			
18. CONCLUSIONS AND RECOMMENDATIONS Approval recommended.			
19. REVIEWER NAME Venelin Iliev, Ph.D.		SIGNATURE 	DATE COMPLETED 10/1/82
DISTRIBUTION ☐		ORIGINAL JACKET ☐	REVIEWER ☐
		DIVISION FILE ☐	

CC: NMK-00
 HFN-120
 HFN-120/V111ev/10-1-82
 R/Dinf. R/Shultz/10-22-82
 F/T:lca:10-22-82; 1tr - Doc 4074B

Oct 29 1982

Chemist Review of NDA 1816.3 October 27, 1982
Periodic Report No. 05 dated 10-13-82

Applicant: Sandoz Pharmaceuticals
East Rutherford N.J. 07073

Name of drug: Restonit (Tencycapam) capsules

Indication: Hypnotic

Comments: Updated Control. and stability capsule to 3
months 2271 Light Radio 3 wk
Instal stability data are satisfactory
Current labeling technically satisfactory

Recommendation: No action indicated

V. J. Liev
Res. Chemist

[Handwritten initials]
10-27-82

cc: NDA 1816-18-163
NFI-120
NUR-00
NFI-120/ULI/10-27-82
RID init RC Shultz/10-27-82/lcc

Chemist Review of NDA 18-163 March 31, 1982
Periodic Reprint # dated 3-1-82

Applicant: Sandoz Pharmaceuticals
Route 10
East Hanover, New Jersey 07936

Name of Drug: Restoril (temazepam) Capsules

Indication: Hypnotic

Comments: Updated controls of the component of the dosage form.
Labeling technically satisfactory (identical to the approved).

Recommendation: No action indicated.

V. Vilev
Venelin Vilev, Ph.D.
Reviewing Chemist

cc:

NMK-DO

~~NEE-120~~

FU-120 Vilev 3/31/82

R/D Init by: RShultz 4/1/82

Received sp 4/2/82

F/T: sp 4/7/82

Doc. Id. 19668

VERSED

18654

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Study No. 126

Title: A Comparison of Midazolam and Diazepam in Combination With Meperidine During Local Anesthesia for Cystoscopy

Investigator: Roy Witherington, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in 40 adult females undergoing cystoscopy for the first time.

Subjects

The study population consisted of 10 females (ASA Status I or II) who were not pregnant and ranged in age from 22 to 62 years. Although 40 patients were projected for this study, it was still in progress at the time of submission. There were 2 females in the midazolam group with a mean age of 52.5 years (range 43-62), 3 in the diazepam group with a mean age of 34.7 years (range 28-39), 3 in the placebo (midazolam) group with a mean age of 43.3 years (range 22-61) and 2 in the placebo (diazepam) group with a mean age of 44.5 years (range 42-47).

Study Drugs: See Study 116

Experimental Design: See Study 116

Results

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.093 mg/kg of midazolam and 0.108 mg/kg of diazepam. Mean times to sedation were 2.2 minutes for midazolam and 3.4 minutes for diazepam.

Physician's Assessment

The assessments for all parameters were "excellent" for midazolam and "fair" to "excellent" for diazepam.

Patient's Assessment

Quality of sedation was rated "good" to "excellent" in both active treatment groups. All patients in these two groups stated that they would undergo a future cystoscopy the same way and all indicated that the procedure was either slightly or not painful.

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Trieger Test

Psychomotor recovery assessment demonstrated an elevation at one hour in both parameters in the midazolam group with return toward baseline at two hours. There was essentially no change in the diazepam scores at either 1 or 2 hours.

Follow-Up Questionnaire for Amnesia

There was no recall of cystoscopy in the midazolam group; whereas, in the diazepam group while no recall of the procedure was present 1 hour later, after 24 hours 2 of 3 patients had clear recall. One patient of 2 in the midazolam group recalled pre-induction procedures whereas in the diazepam group all 3 patients recalled at least 1 pre-induction event.

Safety

The only adverse experiences noted were transient changes in pulse rate and blood pressure. No changes were observed during induction of sedation. All changes were mild or moderate. No patient had evidence of venous irritation.

Summary and Conclusions

This was a randomized, double-blind study which was still in progress at the time of submission. Because only 10 of 40 patients were studied at the time, a statistical analysis of the results was not feasible.

Transient fluctuations in blood pressure and pulse rate were observed but were not considered clinically significant. No patient had evidence of venous irritation following the study.

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Pooled Study Summary

Study Nos. 124, 125, 127, 128, Protocol 2237B

Title: A Comparison of Midazolam and Diazepam In Combination With Meperidine During Local Anesthesia for Cystoscopy

Subjects

Ninety-five males (ASA I or II) undergoing diagnostic cystoscopy for the first time participated in the study. The study population ranged in age from 18 to 96 years. In the midazolam group there were 24 males with a mean age of 60.0 years (range 18-96). In the diazepam group there were 23 males with a mean age of 53.6 years (range 20-78). In the respective placebo groups there were 24 males each, with mean ages of 58.0 years (range 25-82) and 53.4 years (range 24-78).

Results

Differences Among Study Centers

There were no major differences between study centers.

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.104 mg/kg of midazolam and 0.145 mg/kg of diazepam. Midazolam-treated patients required a significantly shorter mean time to reach the sedative end point of 4.2 minutes compared with 5.7 minutes for diazepam patients.

Physician's Assessment

On all of the assessment parameters, midazolam's sedative properties were rated better than placebo. There were no significant differences between the active treatment groups.

Patient's Assessment

On both rating occasions, (one hour after the procedure and on the following day) the active treatment groups rated quality of sedation better than their corresponding placebo groups. On the following day, significantly more midazolam-treated patients stated they would undergo a future procedure the same way than placebo patients. Midazolam-treated patients reported significantly less pain associated with the procedure than patients who received diazepam.

Trieger Test

Both active treatment groups had significantly increased values over baseline in number of dots missed, at one hour, than their corresponding placebo

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groups. Additionally the diazepam group had a significantly elevated total deviation from dots compared with the corresponding placebo group. At two hours no significant differences existed between groups.

Follow-Up Questionnaire for Amnesia

Following test drug administration, both active test groups had diminished recall of the procedure. One hour after cystoscopy midazolam-treated patients had significantly less recall of the procedure compared with diazepam patients. Midazolam-treated patients also had significantly less recall than placebo patients of all events following test drug administration, including the introduction and withdrawal of the cystoscope and the one and two hour post-treatment Trieger Tests.

Patients who received diazepam had significantly less recall of the procedure and of the introduction of the cystoscope compared with placebo patients.

There were some patients in the various groups (more in the active drug groups) who could not recall the administration of the local anesthetic agent.

Safety

Two midazolam and one diazepam patients experienced excessive sedation during or following the procedure. In two cases the investigator felt that the excessive sedation was due to premedication with meperidine. All three patients were given test drug doses that were lower than the mean sedation dose.

One midazolam patient with arteriosclerotic heart disease became unresponsive to painful stimuli and hypotensive, responding to treatment with Narcan.

One midazolam-treated patient developed venous irritation at the injection site for 2 days following the study. A second patient experienced burning and stinging during the injection of midazolam. When the injection was slowed there were no further complaints. Tenderness was observed at the injection site for one day in one placebo (midazolam) patient.

Most changes in vital signs were observed during the maintenance and recovery. Most changes were classified as mild to moderate and were not clinically significant.

Summary

In this multicenter study midazolam when used in combination with meperidine and a topical anesthetic agent was shown to be as safe and effective as diazepam in inducing sedation for cystoscopy. Midazolam-treated patients reported significantly less pain associated with the procedure than diazepam patients. Patients who received midazolam had significantly less recall of the overall procedure and the withdrawal of the cystoscope. There were several cases of excessive sedation from the combination of meperidine and a benzodiazepine.

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Study No. 124

Title: A Comparison of Midazolam and Diazepam In Combination With Meperidine During Local Anesthesia for Cystoscopy

Investigator: William R. Fair, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in male patients premedicated with meperidine for cystoscopy.

Subjects

There were 21 males ranging in age from 24 to 78 years. In the midazolam-treated group there were 5 males with a mean age of 68.0 years (range 63-77). In the diazepam group there were 5 males with a mean age of 64.4 years (range 55-78). In the respective placebo groups there were 6 and 5 male patients with mean age of 60.3 years (range 25-76) and 58.8 years (range 30-76).

Study Drugs: See Study No. 125.

Experimental Design

Randomized, double-blind, placebo controlled, parallel study in 21 male patients. The design of this study was similar to that of study 125 since this was a multicenter study following the same protocol.

Results

This study was still in progress at the time of submission and this report details the results of the first 21 patients.

Deviations from Protocol

Three patients were excluded from all efficacy analyses. Patient (midazolam) became unresponsive to painful stimuli and developed a decrease in blood pressure after receiving 0.758 mg/kg of meperidine and 0.152 mg/kg of midazolam. The cystoscopy was cancelled and 1 ml of Narcan was administered to reverse these effects. Patient (placebo, midazolam) and (placebo, diazepam) experienced pain and discomfort during introduction of the cystoscope; consequently, additional medication was required to complete the procedure. Patient received Valium while patient received Innovar.

The first placebo patient received a total of 10 ml of placebo (midazolam) since the cystoscopist did not think the patient was sufficiently sedated. The person administering the placebo did not want to tell the cystoscopist that placebo was being administered; consequently, the total 10 ml was administered.

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The 24 hour questionnaire for patient who received placebo (midazolam), was not included in the analysis since the questionnaire was completed one month after the procedure. Patient who received diazepam, did not complete the 24 hour questionnaire since additional medication was administered postoperatively for another procedure.

The responses to recall of the Trieger Test of one diazepam-treated patient were not included in analysis. This patient could recall doing only one Trieger Test following cystoscopy but did not know whether it was the one or two hour test. One placebo (midazolam) patient did not answer the question of recall of the two hour Trieger Test.

Induction of Intravenous Sedation

There was no significant difference in mean sedation times between active drugs, although midazolam required a shorter time (5 minutes) compared with diazepam (8 minutes) and a smaller dose (0.081 mg/kg vs. 0.129 mg/kg).

Physician's Assessment

There were no significant differences in these assessments between the active drugs with mean assessments ranging from "good" to "excellent." The patients taking placebo ranged from "poor" to "excellent" with the lowest parameter, in general, being quality of sedation.

Patient's Assessment

All recorded responses for the active drugs with respect to quality of sedation were "good to "excellent." All responding midazolam patients and all but one diazepam patient reported that the cystoscopy was not painful and that they would undergo another procedure the same way.

Trieger Test

The psychomotor recovery pattern was similar in both active treatment groups with elevations from baseline values at 1 hour and return to baseline at two hours.

Follow-Up Questionnaire for Amnesia

None of the patients in the active midazolam group and only one in the diazepam group recalled scope introduction and withdrawal.

Safety

Patient a 65 year old male with a history of chronic obstructive pulmonary disease and arteriosclerotic heart disease became unresponsive to painful stimuli and developed a decrease in blood pressure after receiving 0.759 mg/kg of meperidine and 0.152 mg/kg of midazolam. One milliliter of Diloran was given. The investigator felt that in view of the patient's age and condition, less drug and slower injection would have prevented the adverse effects.

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experienced burning and stinging during the initial injection of midazolam. The drug was injected more slowly without further complaints. No patient had evidence of venous irritation following the study.

Table 1
Clinical Adverse Experiences

	<u>Number of Patients</u>			
	<u>Midaz-</u> <u>olam</u>	<u>Diaz-</u> <u>epam</u>	<u>Placebo</u>	
			<u>Midaz-</u> <u>olma</u>	<u>Diaz-</u> <u>epam</u>
<u>Possibly and Probably Related Drug Effects</u>				
<u>Respiratory System</u>				
Respiration Rate Increase	2	3	2	3
Respiration Rate Decrease	1	0	2	1
<u>Cardiovascular System</u>				
Pulse Increase	1	0	0	1
Pulse Decrease	2	0	2	0
MAP Increase	0	1	0	0
MAP Decrease	1	1	0	0
Pain During Injection of Study Drug	1	0	0	0
<u>Central Nervous</u>				
Unresponsive	1	0	0	0

Most changes in vital signs were transient and were not considered clinically significant.

Summary and Conclusions

This study is still in progress and was not analyzed by the sponsor due to the limited number of patients studied at the time of submission. Midazolam patients experienced better sedation and reported less pain associated with the procedure than placebo patients. The midazolam-treated patients reported the quality of sedation as "good" to "excellent" and none recalled introduction and withdrawal of the cystoscope.

A 65 year old midazolam patient with a history of arteriosclerotic heart disease and clinical condition, less drug and slower injection of the drug would have prevented the adverse effects from occurring.

A midazolam patient complained of burning and stinging at the intravenous injection site. When the drug was injected more slowly there were no further complaints. There were no reports of venous irritation following the study. Transient changes in vital signs were observed.

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Study No. 125

Title: A Comparison of Midazolam and Diazepam In Combination With Meperidine During Local Anesthesia for Cystoscopy

Investigator: Guenter Corssen, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in male patients premedicated with meperidine for cystoscopy.

Subjects

There were 41 males ranging in age from 20 to 96 years. In the midazolam-treated group there were 10 males with a mean age of 56.4 years (range 23-96). In the diazepam group there were 11 males with a mean age of 51.6 years (range 20-76). In the respective placebo groups there were 10 males each, with mean age of 51.6 years (range 25-76) and 47.1 years (range 30-76).

Study Drugs:

Patients were randomly divided into four groups: midazolam, diazepam, placebo to match midazolam and placebo to match diazepam. Thirty minutes prior to cystoscopy, all patients received 35-50 mg of meperidine administered intramuscularly followed by the instillation of topical lidocaine jelly into the urethra 5 to 10 minutes before cystoscopy. Patients assigned to midazolam or diazepam treatment groups received 5.0-7.5 mg of the test medication intravenously over a 2-3 minute period. Elderly patients (as identified by the investigator) received 2.50-3.75 mg of the test medications over the same time interval. Incremental doses (25% of initial dose) were administered, if necessary, until the patient's speech became thickened and slurred but the patient was still responsive to verbal commands. Patients assigned to placebo groups received 2-6 ml total volume of solution administered intravenously over a 5 minute period.

Experimental Design

Randomized, double-blind, controlled, parallel group study in patients undergoing diagnostic cystoscopy for the first time. Immediately following cystoscopy, the physician, who did not know which test medication had been administered, evaluated as excellent, good, fair or poor the sedative effects produced by the test medication. The assessments included: (1) patient cooperation, (2) muscle relaxation, (3) ease of cystoscopic examination, (4) quality of sedation, (5) control of bladder spasms, (6) control of pain, (7) control of retching and vomiting, (8) overall tolerance of the procedure. One hour after cystoscopy and one day later in a follow-up questionnaire, patients

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evaluated the sedation during the procedure as excellent, good, fair, poor. On both occasions patients were asked whether they would elect to undergo a future cystoscopy the same way, if necessary. One hour after cystoscopy, patients evaluated the cystoscopic procedure as not painful, somewhat painful or very painful and whether they could recall none, some or all of the procedure. In the follow-up questionnaire patients were also asked whether they could recall clearly, vaguely or not at all events before, during and after cystoscopy.

Recovery from sedation was assessed by the Trieger Test, which was completed by the patient before medication (baseline) and at 60 and 120 minutes following the cystoscopy. Each Trieger Test was evaluated for the number of dots missed and the total deviation (mm) from the dots.

Blood pressure, respiration rate and pulse rate were monitored before, during and after cystoscopy. Changes in vital signs greater than 20% from baseline were identified as possible adverse experiences. The severity of the changes was categorized as:

mild - a change >20 percent but <30 percent from baseline
moderate = a change >30 percent but <50 percent from baseline
severe = a change >50 percent from baseline or treatment required

Clinical adverse experiences were further categorized according to the phase of the study. The phases of the study were defined as follows:

induction = period of test drug administration
maintenance = period of cystoscopy
recovery = post cystoscopy until discharge

Seven to 14 days following the study, the intravenous injection site was examined for tenderness, redness, and induration.

Results

Deviations from Protocol

Two patients who received midazolam were excluded from all efficacy analyses. Patient #5 had a previous history of drug addiction which he did not admit to until after the study. Patient was unable to comprehend all aspects of the study due to senility.

The Trieger Test results for two patients were not included in efficacy analysis. The test results for patient who received placebo (diazepam) were not returned. There was confusion as to what time the Trieger Tests were completed by one midazolam-treated patient.

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placebo treatment groups. On the 24 hour questionnaire most patients in all treatment groups could recall the baseline Trieger Test and the Administration of local anesthetic. Most midazolam-treated patients had no recall of the introduction and withdrawal of the cystoscope. When compared to placebo, midazolam treated patients had significantly less recall of the withdrawal of the cystoscope. Most patients who received midazolam placebo could recall both the introduction and withdrawal of the cystoscope. About half of the patients who received diazepam and placebo had no recall of the introduction and withdrawal of the cystoscope. Most patients in all groups could recall the post-treatment Trieger Tests.

Safety

A 96 year old male with Alzheimer's disease experienced excessive sedation following the procedure. This patient received 0.833 mg/kg of meperidine and 0.083 mg/kg of midazolam. The investigator felt that the excessive sedation was probably due to the dosage of meperidine administered.

There were no reports of venous irritation following the study in any of the treatment groups.

Table 1
Clinical Adverse Experiences

	Number of Patients			
	Midaz- olam	Diaz- epam	Placebo Midaz- olma	Placebo Diaz- epam
<u>Possibly and Probably Related Drug Effects</u>				
<u>Respiratory System</u>				
Respiration Rate Increase	1	2	4	2
Respiration Rate Decrease	4	2	0	1
<u>Cardiovascular System</u>				
Pulse Increase	1	2	0	1
Pulse Decrease	0	1	1	0
MAP Increase	1	2	1	0
MAP Decrease	2	1	1	1
<u>Remotely Related Drug Effect</u>				
<u>Miscellaneous</u>				
Excessive Sedation	1	0	0	0

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One midazolam, three diazepam, and one placebo (diazepam) did not return the 24 hour patient questionnaires. Several patients also omitted answering questions on the 24 hour questionnaire,

- placebo (midazolam) - recall scope introduction
- midazolam - recall two hour Trieger Test
- midazolam - recall one and two hour Trieger Test
- placebo (diazepam) - recall two hour Trieger Test

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.133 mg/kg of midazolam and 0.187 mg/kg of diazepam. The mean time to reach the sedative end point was comparable between midazolam and diazepam groups.

Physician's Assessment

The physician's assessments were in most instances "good" to "excellent" for midazolam and diazepam treatment groups, while assessments of sedation for patients in the placebo groups, with the exception of patient cooperation, and control of retching and vomiting, were "poor" to "fair." These latter two parameters were rated as "excellent" or "good" in all 4 groups. Both active treatment groups were evaluated significantly better than their respective placebo groups except as noted above.

Patient's Assessment

There were no significant differences between actual treatment groups or between diazepam and placebo on rating the quality of sedation or willingness to undergo the procedure the same way again. On the two test occasions, one hour after the procedure and on the following day, midazolam treated patients evaluated sedation significantly better than placebo patients. On the following day significantly more midazolam patients were willing to undergo the procedure the same way. There were no significant differences among the treatment groups for pain associated with the cystoscopy.

Trieger Test

On both the one and two hour post-treatment Trieger Tests, midazolam-treated patients had a significantly increased number of dots missed and deviations from the dots compared with patients who received placebo. Patients in the midazolam, diazepam and diazepam placebo groups all missed more dots on the one and two hour post treatment Trieger Tests than at baseline.

Follow-Up Questionnaire for Amnesia

One hour after cystoscopy midazolam and diazepam treatment groups had significantly less recall of the procedure when compared with their respective

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Most changes in vital signs were transient and were not considered clinically significant. Changes in vital signs were usually mild to moderate with very few classified as severe. A severe increase in pulse rate during cystoscopy was observed in one diazepam treated patient. Severe decreases in respiration rate during cystoscopy were also observed in one midazolam patient and one diazepam patient.

Summary and Conclusions

This randomized, double-blind study compared the use of IV midazolam with IV diazepam and placebo to provide sedation during cystoscopy. As adjuncts to topical anesthesia and intramuscular meperidine both midazolam and diazepam were effective sedative agents. The physician's assessments were in most cases "good" to "excellent" for both active treatment groups while assessments of most sedation parameters in the placebo groups were "fair" to "poor." The active treatment groups were evaluated significantly better than their corresponding placebo groups on all of the physician's assessments, except for control of retching and vomiting and patient cooperation which were rated as "good" or "excellent" in all 4 groups.

Midazolam patients rated quality of sedation significantly better than the placebo, as well as having significantly more patients willing to undergo a future procedure the same way and significantly less patients had recall of the overall procedure and the withdrawal of the cystoscope. There were no significant differences between active treatment and placebo on the patient's assessments of the procedure. One hour after the procedure, diazepam patients had significantly less recall of the procedure than did the corresponding placebo-treated patients.

With respect to psychomotor recovery, the midazolam-treated patients showed a significantly greater number of dots missed and deviation from the dots on the post-treatment Trieger Tests when compared with placebo.

Transient fluctuations in vital signs were observed in all treatment groups but were not considered clinically significant. A 96 year old midazolam patient developed excessive sedation following the procedure but this was felt by the investigator to be related to the dose of meperidine. There was no venous irritation.

This study showed that midazolam, when used in combination with meperidine and a local anesthetic agent, is as safe and effective as diazepam in inducing sedation intravenously for cystoscopy.

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Study No. 127

Title: A Comparison of Midazolam and Diazepam In Combination With Meperidine During Local Anesthesia for Cystoscopy

Investigator: Philip H. Hanno, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in adult males premedicated with meperidine for cystoscopy.

Experimental Design

Randomized, double-blind, placebo and reference drug controlled study in patients undergoing diagnostic cystoscopy for the first time.

Subjects

There were 14 males ranging in age from 55 to 76 years. The midazolam-treated group there were 4 males with a mean age of 66.5 years (range 60-76). In the diazepam group there were 3 males with a mean age of 59.0 years (range 58-60).

In the respective placebo groups there were 3 and 4 males with mean ages of 62.0 years (range 57-69) and 60.5 years (range 55-70).

Study Drugs: See Study 125.

Results

Fourteen of forty patients were recruited into the study by the time of submission.

Deviations from Protocol

Two patients in each placebo group were excluded from efficacy analyses because each required 10 mg of diazepam to complete the procedure because of pain and discomfort experienced during introduction of the cystoscope.

Induction of Intravenous Sedation

Comparable levels of sedation were achieved during similar time intervals with mean doses of 0.089 mg/kg of midazolam and 0.145 mg/kg of diazepam.

Physician's Assessment

Similar assessments for all parameters were made for both active treatment groups.

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Patient's Assessment

Similar assessments were made for both active treatment groups.

Trieger Test

Patterns of psychomotor recovery were dissimilar for both active treatment groups with maximum elevations from baseline in number of dots missed and total deviation from dots at one hour with return to baseline for the midazolam group and maximum elevations from baseline at two hours in the diazepam group.

Follow-Up Questionnaire for Amnesia

No patients in the midazolam group recalled scope introduction and withdrawal on the following day, although 1 recalled cystoscopy one hour after the procedure.

Safety

The only adverse experiences observed were mild increases in mean arterial pressure and pulse rate during cystoscopy. No changes in vital signs were observed during induction of sedation or recovery. All changes in vital signs were transient and were not considered clinically significant. No patient had evidence of irritation at the intravenous site following the study.

Summary and Conclusions

The sponsor did not undertake a statistical analysis of the study due to the limited number of patients studied (14 of 40) at the time of submission. Transient fluctuations in blood pressure and pulse rate were observed but were not considered clinically significant. There was no venous irritation.

000084

Study No. 128

Title: A Comparison of Midazolam and Diazepam Administered Intravenously With Local Anesthesia for Cystoscopy

Investigator: Russell Lawson, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in adult males premedicated with meperidine for cystoscopy.

Experimental Design

Randomized, double-blind, placebo and reference drug controlled study in patients undergoing diagnostic cystoscopy for the first time.

Subjects

There were 19 males ranging in age from 18 to 82 years. In the midazolam group there were 5 males with a mean age of 54.0 years (range 18-82). In the diazepam group there were 4 males with a mean age of 68.0 years (range 62-78). In the respective placebo groups there were 5 males each with mean ages of 65.4 years (range 53-82) and 55.0 years (range 24-73).

Study Drugs: See Study 125.

Results

Nineteen of forty patients were recruited into the study by the time of submission.

Deviations from Protocol

One patient who received placebo (diazepam) was excluded from the efficacy evaluation for receiving an excludable concomitant medication (Ativan) within 24 hours of the procedure.

The Trieger Test results of two are not included. Patient , who received placebo (midazolam), did not understand the directions for completing the test. Patient , who received diazepam, had Parkinson's disease.

Induction of Intravenous Sedation

Comparable levels of sedation were obtained with mean doses of 0.089 mg/kg midazolam and 0.052 mg/kg diazepam. The active treatment groups reached the sedative end point in comparable mean times (3.0 minutes, midazolam, 2.6 minutes diazepam).

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Physician's Assessment

Similar "good" to "excellent" results were produced in both active treatment groups.

Patient's Assessment

"Good" to "excellent" ratings were achieved for both active drug groups one hour after the procedure and on the following day. All patients in both active treatment groups said they would elect to undergo a future procedure the same way. All midazolam patients said there was no pain associated with the cystoscopy, whereas, 3 of 4 diazepam patients noted some pain during the procedure.

Trieger Test

The two active treatment groups showed similar patterns of psychomotor recovery, with elevations from the baseline in number of dots missed and total deviation from the dots at 1 hour and return toward baseline at two hours.

Follow-Up Questionnaire for Amnesia

There was no recall of scope introduction and withdrawal in either active treatment group.

Safety

An 81 year old patient who received 1.14 mg/kg of meperidine and 0.057 mg/kg of midazolam developed excessive sedation during the cystoscopy. No corrective measures were required. Patient who received midazolam, developed tenderness, redness and induration at the intravenous injection site for 2 days following the study.

A 78 year old patient with a history of cerebral vascular disease, experienced excessive sedation after receiving 0.77 mg/kg of meperidine. Because of this the patient received only 0.2 ml (0.016 mg/kg) of diazepam.

Patient who received placebo (midazolam) experienced dry mouth which was attributed to meperidine. Patient who also received placebo (midazolam), experienced tenderness for one day following the study.

A placebo (diazepam) treated patient with a history of arteriosclerotic vascular disease, experienced dizziness upon arising from bed one hour after the cystoscopy. His blood pressure, which was 126/67 mmHg before cystoscopy, increased to 181/108 mmHg during the procedure and decreased to 88/68 mmHg one hour after cystoscopy.

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Table 1
Clinical Adverse Experiences

	<u>Number of Patients</u>			
	<u>Midaz- olam</u>	<u>Diaz- epam</u>	<u>Midaz- olam</u>	<u>Diaz- epam</u>
<u>Possibly and Probably Related Drug Effects</u>				
<u>Respiratory System</u>				
Respiration Rate Increase	3	3	3	3
Respiration Rate Decrease	2	1	3	3
<u>Cardiovascular System</u>				
Pulse Increase	2	0	0	0
Pulse Decrease	1	0	2	2
MAP Increase	0	0	1	2
MAP Decrease	2	1	0	1
Tenderness of Vein	1	0	1	0
Redness of Vein	1	0	0	0
Induration of Vein	1	0	0	0
<u>Gastrointestinal</u>				
Dry Mouth	0	0	1	0
<u>Spinal Senses</u>				
Dizziness	0	0	0	1
<u>Miscellaneous</u>				
Excessive Sedation	1	0	0	0
<u>Remotely Related Drug Effect</u>				
<u>Miscellaneous</u>				
Excessive Sedation	0	1	0	0

Most changes in vital signs were classified as mild or moderate. Several patients in various treatment groups had severe changes in vital sign measurements but these changes were not considered to be clinically significant.

Summary and Conclusions

A statistical analysis of this study was not undertaken due to the limited number of patients studied (19 of 40) by the time of submission. One elderly midazolam patient and one elderly diazepam patient experienced excessive

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sedation probably related to too high a dose of meperidine premedication. One placebo (diazepam) patient experienced dizziness upon arising, related to hypotension, one hour following cystoscopy. Following the study venous irritation was observed in one placebo (midazolam) and one midazolam-treated patient. Transient fluctuations in vital signs were observed but were not considered clinically significant.

Pooled Study Summary

Study Nos. 101, 110, 120, Protocol 2233A

Title: A Comparison of Midazolam and Diazepam Administered Intravenously With Local Anesthesia for Gastroscopy

Subjects

One hundred nine patients (ASA I or II) undergoing diagnostic gastroscopy for the first time participated in the study. The study population consisted of 29 non-pregnant females and 80 males ranging in age from 19 to 74 years. In the midazolam group there were 54 patients comprised of 39 males and 15 females with a mean age of 49.1 years (range 19-73). In the diazepam group there were 55 patients comprised of 41 males and 14 females with a mean age of 47.4 years (range 23-74).

Results

Differences Among Study Centers

Dr. Isenberg's study (#120) was not included in efficacy analyses because the drug shipment was divided incorrectly between two study sites. This resulted in compromised randomization since drug codes were not assigned in date order. The study was included in the pooled safety analyses.

There were differences between centers in the dose of midazolam or diazepam required for induction of sedation. Patient's in Dr. Lanza's study (#101) required approximately twice as much midazolam to reach the sedative end point as did patients in the other two studies.

Induction of Intravenous Sedation

Comparable levels of sedation were attained with mean doses of 0.164 mg/kg of midazolam and 0.264 mg/kg of diazepam. Midazolam-treated patients required a significantly shorter mean time to reach the sedative end point of slurred speech than did diazepam patients (2.8 vs. 4.8 minutes).

Physician's Assessment

The physician's assessment of sedation was the same for both test medications except that diazepam-treated patients experienced significantly better muscle relaxation and were more cooperative.

Patient's Assessment

These were comparable between test groups, except patients who received midazolam reported significantly less pain associated with the gastroscopy.

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Trieger Test

Recovery from sedation as measured by this test was comparable between treatment groups.

Follow-Up Questionnaire for Amnesia

Following test drug administration, midazolam-treated patients had significantly less recall of the introduction and withdrawal of the gastroscope. There were also significantly more midazolam patients with diminished recall of the one and two hour post-treatment Trieger Tests.

Safety

Four midazolam and 7 diazepam-treated patients had evidence of irritation at the intravenous injection site at the follow-up examination. There were several reports of drowsiness, dizziness, weakness and lethargy in each group, but they were associated with the high doses of test drug received by patients at one study center. There were no clinically significant changes in vital signs.

Summary and Conclusions

In this multicenter study midazolam was demonstrated to be as safe and effective as diazepam in inducing sedation for gastroscopy when administered as an adjunct to topical anesthesia. Patients who received midazolam were more relaxed, had less pain and had diminished recall of the procedure.

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Study No. 101

Title: A comparison of Midazolam and Diazepam Administered Intravenously With Local Anesthesia for Gastroscopy

Investigator: Frank L. Lanza, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in patients undergoing gastroscopy for the first time.

Experimental Design

Randomized, double-blind parallel study in 27 patients. The design of this study was similar to that of study 110 since this was a multicenter study following the same protocol.

Subjects

There were 19 non-pregnant females and 8 males ranging in age from 23 to 67 years. In the midazolam group there were 4 males and 10 females with a mean age of 40.2 years (range 23-62). In the diazepam group there were 4 males and 9 females with a mean age of 44.1 years (range 48-140).

Study Drugs: See Study 110.

Results

Deviations from Protocol

One diazepam-treated patient did not return the 24 hour patient questionnaire. Patient (diazepam) did not evaluate quality of sedation on the 24 hour questionnaire. Midazolam patient did not complete the two hour post-treatment Trieger Test.

Induction of Intravenous Sedation

Comparable levels of sedation were obtained with mean doses of 0.225 mg/kg midazolam and 0.366 mg/kg diazepam. Midazolam-treated patients reached the sedative end point almost twice as fast as the diazepam group (mean 3.13 vs. 6.08); the difference was statistically significant for gastroscopies of similar duration.

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Physician's Assessment

There were no statistically significant differences between treatments in the physician's assessment of sedation. The assessment was "fair" to "good" for both groups in most instances.

Patient's Assessment

All patients in both test groups rated sedation as "good" or "excellent" on both rating periods. Both test groups had little or no pain associated with the gastroscopy and most patients were willing to undergo the procedure the same way again.

Trieger Test

One hour following the procedure, midazolam patients had a significantly greater number of dots missed and total deviation from the dots compared with the diazepam group. At two hours the results were similar.

Follow-up Questionnaire for Amnesia

All patients in both groups recalled the events prior to administration of the test drug. No patient in either group recalled the introduction and withdrawal of the scope. The midazolam patients also had significantly less recall of the one and two hour post treatment Trieger Tests.

Safety

Patient who received 0.217 mg/kg of midazolam, was lethargic, weak and dizzy for several hours following the study. The patient had a history of hypoglycemia and hypothyroidism.

One diazepam patient developed weakness after the study. This patient who was on chronic diazepam therapy for anxiety, required 0.738 mg/kg of diazepam to sedate. Technically this case does not represent a protocol violation since, according to the case record, diazepam was discontinued 2 days prior to the procedure. It would have been prudent if the investigator had excluded the subject, who was taking diazepam 2.5 mg t.i.d. on a chronic basis. Patient who also received diazepam, had a headache and felt nauseated the evening following the procedure, while another diazepam-treated patient was lethargic following the gastroscopy.

Two midazolam patients (.203 mg/kg and .206 mg/kg) and one diazepam patient experienced drowsiness following the study, which may well have been related to the high doses of test drugs which were administered to the patients in this study.

One patient in each treatment group (- midazolam and - diazepam) showed evidence of venous irritation following the study.

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Table 1
Clinical Adverse Experiences

	<u>Midazolam</u>		<u>Diazepam</u>	
	<u># pts.</u>	<u>Percent</u>	<u># pts.</u>	<u>Percent</u>
<u>Possibly and Probably Related Drug Effects</u>				
<u>Respiratory System</u>				
Respiration Rate Increase	8	57.1	4	30.8
Respiration Rate Decrease	1	7.1	2	15.4
<u>Cardiovascular System</u>				
Pulse Increase	5	35.7	6	46.2
Pulse Decrease	1	7.1	1	7.7
HAP Increase	2	14.3	2	15.4
Tenderness of Vein	1	7.1	0	0
Induration of Vein	0	0	1	7.7
<u>Gastrointestinal</u>				
Nausea	0	0	1	7.7
<u>Central Nervous</u>				
Headache	0	0	1	7.7
<u>Special Sense</u>				
Dizziness	1	7.1	0	0
<u>Miscellaneous</u>				
Apathy	0	0	1	7.7
Drowsy	2	14.3	1	7.7
Lethargy	1	7.1	0	0
Weak	1	7.1	1	7.7
<u>Remotely Related Drug Effect</u>				
<u>Gastrointestinal</u>				
Throat-Pain	0	0	1	7.7

Most changes in vital signs were transient and were most often associated with the gastroscopy. Changes were usually mild or moderate with very few classified as severe. Severe increases in respiration and pulse rate were observed in several patients in both treatment groups.

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Summary and Conclusions

This randomized, double-blind study compared the use of IV midazolam with IV diazepam to provide sedation during gastroscopy. The study, at the time of submission, was still in progress, and this submission represents an interim report of the first 27 patients. As adjuncts to local anesthesia, both drugs were effective intravenous sedative agents for gastroscopy. Physician's assessments of sedation were "fair" to "good" in most instances. All patients rated sedation "good" or "excellent" and reported little or no pain associated with the procedure.

Failure to recall the introduction and withdrawal of the gastroscope was induced in all patients. This was extended out for 2 hours with respect to recall of the post-treatment Trieger Tests by 64% of the midazolam-treated patients. On the one hour Trieger Test midazolam patients had a significantly higher increase in number of dots missed and total deviation from the dots, compared with the diazepam-treated patients. By two hours these results had returned to near the baseline value.

One patient in each treatment group had signs of venous irritation following the study. Transient fluctuations were observed in both treatment groups but were not considered clinically significant. One diazepam patient had a headache and felt nauseated following the procedure.

Several patients in each group experienced weakness, drowsiness or lethargy following the study. These side effects were probably related to the relatively high doses of both study drugs administered in this study.

This study showed that midazolam, when used in combination with a local anesthetic agent, is as safe and effective as diazepam in inducing sedation for gastroscopy. Patients who received midazolam had no recall of the introduction and withdrawal of the gastroscope and many had impaired recall of the post-treatment Trieger Tests.

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Summary and Conclusions

This randomized, double-blind study compared the use of IV midazolam with IV diazepam to provide sedation during gastroscopy. The study, at the time of submission, was still in progress, and this submission represents an interim report of the first 27 patients. As adjuncts to local anesthesia, both drugs were effective intravenous sedative agents for gastroscopy. Physician's assessments of sedation were "fair" to "good" in most instances. All patients rated sedation "good" or "excellent" and reported little or no pain associated with the procedure.

Failure to recall the introduction and withdrawal of the gastroscope was induced in all patients. This was extended out for 2 hours with respect to recall of the post-treatment Trieger Tests by 64% of the midazolam-treated patients. On the one hour Trieger Test midazolam patients had a significantly higher increase in number of dots missed and total deviation from the dots, compared with the diazepam-treated patients. By two hours these results had returned to near the baseline value.

One patient in each treatment group had signs of venous irritation following the study. Transient fluctuations were observed in both treatment groups but were not considered clinically significant. One diazepam patient had a headache and felt nauseated following the procedure.

Several patients in each group experienced weakness, drowsiness or lethargy following the study. These side effects were probably related to the relatively high doses of both study drugs administered in this study.

This study showed that midazolam, when used in combination with a local anesthetic agent, is as safe and effective as diazepam in inducing sedation for gastroscopy. Patients who received midazolam had no recall of the introduction and withdrawal of the gastroscope and many had impaired recall of the post-treatment Trieger Tests.

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Study No. 110

Title: A comparison of Midazolam and Diazepam Administered Intravenously With Local Anesthesia for Gastroscopy

Investigator: George Dewey Dunn, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in patients undergoing gastroscopy for the first time.

Experimental Design

Randomized, double-blind parallel study in 41 adults undergoing gastroscopy. Prior to gastroscopy, midazolam or diazepam was administered by randomized assignment. Immediately following the gastroscopy, the physician evaluated as excellent, good, fair or poor the sedative effects produced by the test medication. The assessments included (1) patient cooperation, (2) muscle relaxation, (3) ease of gastroscopic examination, (4) control of gag reflex, (5) control of laryngospasm, (6) control of cough reflex, (7) control of retching and vomiting, (8) control of salivation and (9) overall tolerance of the procedure. One hour after gastroscopy and one day later in a follow up questionnaire, patients evaluated the sedative during the procedure as excellent, good, fair or poor. On both occasions patients were asked whether they would elect to undergo a future gastroscopy the same way. One hour after the procedure, patients evaluated the procedure as not painful, somewhat painful or very painful and whether they could recall none, some or all of the gastroscopy. In the follow-up questionnaire, patients were asked about their level of recall of events before, during and after gastroscopy.

Recovery from sedation was assessed by the Trieger Test which was administered before medication (baseline) and at 60 and 120 minutes after the procedure. Each test was evaluated for the number of dots missed and the total deviation (mm) from the dots.

Vital signs were monitored before, during and after gastroscopy. Changes greater than 20% from baseline were identified as possible adverse experiences, and were categorized according to the phase of the study as induction, maintenance or recovery. Seven to 14 days following the study, the intravenous injection site was examined for tenderness, redness and induration.

Subjects

There was 1 non-pregnant female and 40 males ranging in age from 27 to 70 years (ASA status I or II). In the midazolam group there were 19 males and 1 female with a mean age of 51.8 years (range 27-67). In the diazepam group there were 21 males with a mean age of 48.7 (range 30-70).

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Study Drugs

Approximately 30 minutes before the gastroscopy, atropine 0.5 mg was administered intramuscularly. Following topical anesthetic administration, 10-15 mg of either midazolam or diazepam was administered intravenously over a 2-3 minutes period. Elderly patients (as identified by the investigator) received 5.0 - 7.4 mg of the test medications over the same time interval. Incremental doses (25% of initial dose) were administered, if necessary, until the patients speech became slurred.

Results

Deviations from Protocol

The physician's assessment of the procedure and the one hour-patient questionnaire were not obtained for patient of the diazepam group. Patient of the midazolam group was unable to complete the Trieger Tests due to poor vision.

Induction of Intravenous Sedation

Comparable levels of sedation were obtained with mean doses of 0.103 mg/kg of midazolam and 0.161 mg/kg of diazepam. The average time to reach the sedative end point was 2.39 and 3.56 minutes for midazolam and diazepam, respectively, with similar duration of procedures.

Physician's Assessment

The physician's assessment of sedation was "good" to "excellent" for both groups of patients. There were no statistically significant differences between treatments.

Patient's Assessment

After the procedure and the following day all midazolam and 95% of the diazepam patients rated the sedation "good" or "excellent." Significantly more diazepam-treated patients found the gastroscopy "somewhat painful." All patients indicated one hour after the procedure that they would have a future gastroscopy done the same way; and, on the following day, all midazolam and 95% of the diazepam patients responded affirmatively.

Trieger Test

There were no significant differences between groups in recovery from sedation. There was an increase in number of dots missed and total deviation from the dots compared with the baseline in both groups one hour after the gastroscopy with a trend toward return to baseline at two hours.

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Follow-Up Questionnaire for Amnesia

Most patients could recall events prior to test drug administration. Significantly more midazolam-treated patients had no recall of the introductions and withdrawal of the gastroscope and of the one hour Trieger Test. Recall of the two hour Trieger Test was not significantly different between groups and was present in most of the patients.

Safety

On the day following the procedure, patient (diazepam) developed conjunctivitis and on day three there was a rash on both legs and a swelling of the left axilla.

Patient (midazolam) experienced severe chest pain due to a dilated esophagus. This patient also was drowsy following the procedure. One midazolam patient, and two diazepam patients experienced mild headaches following the procedure. Patient - diazepam was dizzy following the procedure.

Two midazolam-treated patients had venous irritation on the follow-up examination. Four diazepam-treated patients also had venous irritation.

Most changes in vital signs were transient and were most often associated with the gastroscopy. One change was observed during induction in which one diazepam patient had a mild increase in pulse rate. Most changes were mild to moderate.

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Table 1

Clinical Adverse Experiences

	<u>Midazolam</u>		<u>Diazepam</u>	
	<u># pts.</u>	<u>Percent</u>	<u># pts.</u>	<u>Percent</u>
<u>Probably and Possibly Related Drug Effects</u>				
<u>Respiratory System</u>				
Respiration Rate Increase	3	15.0	6	28.6
Respiration Rate Decrease	5	25.0	3	14.3
<u>Cardiovascular System</u>				
Pulse Increase	10	50.0	6	28.6
Pulse Decrease	0	0	3	14.3
MAP Increase	3	15.0	8	38.1
MAP Decrease	5	25.0	5	23.8
Tenderness of Vein	0	0	2	9.5
Redness of Vein	1	5.0	1	4.8
Induration of Vein	1	5.0	2	9.5
<u>Integumentary</u>				
Rash on legs	0	0	1	4.8
Swollen armpit	0	0	1	4.8
<u>Special Sense</u>				
Conjunctivitis	0	0	1	4.8
Dizziness	0	0	1	4.8
<u>Central Nervous</u>				
Headache	1	5.0	1	4.8
<u>Miscellaneous</u>				
Drowsy	1	5.0	0	0
<u>Remotely Related Drug Effect</u>				
<u>Respiratory System</u>				
Sore throat	1	5.0	0	0
<u>Gastrointestinal</u>				
Dry mouth	1	5.0	0	0
<u>Central Nervous</u>				
Headache	0	0	1	4.8
<u>Miscellaneous</u>				
Chest pain	1	5.0	1	4.8

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Summary and Conclusions

This randomized double-blind study compared the use of IV midazolam with IV diazepam to provide sedation during gastroscopy. As adjuncts to topical anesthesia, both agents were effective sedative agents. Assessments of sedation were "good" to "excellent" for both test medications. Significantly more diazepam patients found the gastroscopy "somewhat painful." One hour following the procedure all patients indicated that they would undergo the gastroscopy the same way again, and these responses were nearly duplicated on the following day.

There were no significant differences between treatments on the Trieger Test; however, both groups showed some impairment of performance one hour after the procedure with return toward baseline at two hours. Midazolam-treated patients had significantly less recall of the introduction and recall of the gastroscope as well as the one hour post-treatment Trieger Test.

One patient who received diazepam developed conjunctivitis, a rash on both legs, and swelling of the left axilla. One midazolam and two diazepam patients had mild headaches following the gastroscopy. Two midazolam and four diazepam patients had venous irritation at the injection site following the study. Transient fluctuations in vital signs were observed in both treatment groups but were not considered clinically significant.

This study showed that midazolam, when used in combination with a local anesthetic agent, is as safe and effective as diazepam in inducing sedation intravenously for gastroscopy. Midazolam was more effective in inducing diminished recall of the procedure.

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Study No. 120

Title: A comparison of Midazolam and Diazepam Administered Intravenously With Local Anesthesia for Gastroscopy

Investigator: Jon I. Isenberg, M.D.

Objective

The objective of this study was to compare the sedative and amnestic properties of intravenous midazolam and diazepam in patients undergoing gastroscopy for the first time.

Experimental Design

Randomized, double-blind parallel study in 41 adults. The design of this study was similar to that of study 110 since this was a multicenter study following the same protocol.

Subjects

There were 9 non-pregnant females and 32 males ranging in age from 19 to 74 years (ASA status I or II). In the midazolam group there were 16 males and 4 females with a mean age of 52.7 (range 19-73). In the diazepam group there were 16 males and 5 females with a mean age of 48.2 years (range 25-74).

Study Drugs: See Study 110.

Results

Deviations from Protocol

Midazolam patient was excluded from all efficacy analyses since the patient received an excluded concomitant medication (thioridazine) on the day of the study. This patient was included in all analyses of safety.

One midazolam patient refused to stay for the two hour Trieger Test. No weight was recorded for patient who received 4.5 mg of midazolam.

Several patients omitted answering a question on the 24 hour questionnaire.

- #1 (Midazolam) - Quality of sedation
- #1 (Midazolam) - Future procedure done same way
- #13 (Diazepam) - Recall withdrawal of gastroscop
- #33 (Midazolam) - Recall withdrawal of gastroscop
- #35 (Diazepam) - Future procedure done same way
- #46 (Diazepam) - Quality of sedation

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Induction of Intravenous Sedation

Comparable levels of sedation were obtained with mean doses of 0.117 mg/kg of midazolam and 0.198 mg/kg of diazepam. One midazolam patient required an additional dose of 0.063 mg/kg to maintain sedation. Midazolam-treated patients required a significantly shorter time to reach the sedative end point (3.2 vs. 5.9 minutes), with similar average duration of gastroscopies.

Physician's Assessment

The physician's assessments of sedation were in most instances "fair" to "excellent" for both treatment groups. There were no significant intergroup differences in the assessment.

Patient's Assessment

The majority of patients rated the sedation produced by either drug as "good" or "excellent." Both groups reported little or no pain associated with the gastroscopy. Most patients were willing to undergo the procedure the same way again.

Trieger Test

There were no significant differences between treatment groups in recovery from sedation. Both groups showed a slight increase in number of dots missed and total deviation from the dots one hour after the gastroscopy. By two hours, the results had returned to near the baseline values.

Follow-Up Questionnaire for Amnesia

Most patients in both groups recalled the events which preceded test drug administration. Although there was no significant difference between groups in recall of the procedure one hour later, on the following day, significantly less midazolam-treated patients had recall of the introduction and withdrawal of the gastroscope than those who received diazepam. The majority of the patients in both groups recalled both post-treatment Trieger Tests.

Safety

Patient 1 who received 0.157 mg/kg of midazolam was argumentative during the gastroscopy; therefore, an additional 5 mg was administered to calm the patient. Induration of the intravenous injection site was also observed in this patient for one week following the study.

Several days following the study, one diazepam patient developed tinnitus which lasted for 3 days. Another diazepam patient had a supraorbital headache for one week following the study. These reactions were considered to be remotely related to the administration of diazepam.

Two diazepam patients had evidence of venous irritation following the study.

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Table 1
Clinical Adverse Experiences

	<u>Midazolam</u>		<u>Diazepam</u>	
	<u># pts.</u>	<u>Percent</u>	<u># pts.</u>	<u>Percent</u>
<u>Possibly and Probably Related Drug Effects</u>				
<u>Cardiovascular System</u>				
Pulse Increase	7	35.0	14	66.7
Pulse Decrease	3	15.0	4	19.0
MAP Increase	4	20.0	2	9.5
MAP Decrease	4	20.0	2	9.5
Tenderness of Vein	0	0	2	9.5
Induration of Vein	1	5.0	1	4.8
<u>Integumentary</u>				
Inflammation at injection site	0	0	1	4.8
<u>Miscellaneous</u>				
Argumentative	1	5.0	0	0
<u>Remotely Related Drug Effect</u>				
<u>Central Nervous</u>				
Headache	0	0	1	4.8
<u>Special Sense</u>				
Tinnitus	0	0	1	4.8

Most changes in vital signs were transient and were not considered clinically significant. One midazolam-treated patient had a severe increase in mean arterial pressure during the gastroscopy. A severe increase in pulse rate was observed in several patients in both groups during gastroscopy and recovery.

Summary and Conclusions

This randomized, double-blind study compared the use of IV midazolam with IV diazepam to provide sedation during gastroscopy. As adjuncts to topical anesthesia, both agents were effective sedative agents. Assessments of sedation by the physician were "fair" to "excellent" in most instances. Most patients rated the quality of sedation as "good" or "excellent" and both groups reported little or no pain associated with the gastroscopy. Most patients were willing to undergo a future gastroscopy the same way again.

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Most patients recalled events prior to gastroscopy. While there was no difference between groups one hour after the procedure, significantly more midazolam patients had no recall of the gastroscope introduction and withdrawal on the following day. Most patients had recall of all the Trieger Tests. Recovery from sedation as assessed by the Trieger Tests was comparable between groups.

One midazolam patient became argumentative during the procedure and an additional dose of the drug was given. Induration of the intravenous site was also seen in this patient.

With respect to diazepam-treated patients, one complained of tinnitus for several days while another had a supraorbital headache lasting for a week. These were considered remotely related to the treatment. Two patients had venous irritation at the injection site. Transient changes in vital signs were observed in both groups but were not considered clinically significant.

This study showed that midazolam, when used in combination with a local anesthetic agent, is as safe and effective as diazepam in inducing sedation for gastroscopy. Midazolam was more effective in inducing diminished recall of the procedure.

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Pooled Study Summary

Study Nos. 102, 104, Protocol 2239A

Title: A Comparison of Midazolam and Diazepam in Combination With Meperidine During Local Anesthesia for Gastroscopy

Subjects

Forty-one patients (ASA Status I or II) undergoing coronary angiography were the subjects of this study. The study population was comprised of 15 non-pregnant females and 26 males ranging in age from 20 to 76 years. In the midazolam group there were 21 subjects comprised of 10 males and 11 females with a mean age of 50.5 years (range 20-76). In the diazepam group there were 20 subjects comprised of 16 males and 4 females with a mean age of 51.7 years (range 21-73).

Results

Differences Between the Centers

The protocol specified that all patients were to receive 50 mg of meperidine with this dose adjusted when necessary to match special requirements of the patients (age, weight, debility). Dr. White administered meperidine at a dose of 1 mg/kg to all patients in his study without considering the patient's age or condition. Several patients in his study experienced extended periods of drowsiness (up to 100 minutes) following the completion of the study. This was believed to be related to the combined effects of a 1 mg/kg dose of meperidine administered concomitantly with midazolam or diazepam.

Induction of Intravenous Sedation

Comparable levels of intravenous sedation were attained with mean doses of 0.095 mg/kg of midazolam and 0.180 mg/kg of diazepam. Two patients in Dr. White's study (one in each treatment group) required maintenance sedation doses for completion of the procedure.

Midazolam patients required a significantly shorter mean time (4.3 minutes) to reach the sedative end point than did diazepam patients (6.1 minutes).

Physician's Assessment

In most instances the physicians' assessments of the sedative properties of the test drugs were "good" to "excellent". Diazepam-treated patients had significantly better control of retching and vomiting.

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Patient's Assessment

On both rating occasions (1 hour after the procedure and the following day) all diazepam and 95% of midazolam-treated patients rated sedation as "good" or "excellent". Most patients in both treatment groups reported little or no pain associated with the gastroscopy, although 5% of the midazolam group reported the procedure as "very painful". All the diazepam and 95% of the midazolam group were willing to have a future procedure done the same way again.

Trieger Test

There were increases in number of dots missed and deviations from the dots in both treatment groups one hour following the procedure. At two hours these values had returned toward the baseline values.

Follow-Up Questionnaire for Amnesia

Most patients in both groups could recall all events which occurred prior to test drug administration. Following test drug administration the majority of patients in both groups had diminished recall of the procedure. A significantly larger number of midazolam patients had diminished recall of the one hour Trieger Test than in the diazepam group.

Safety

- A remotely related to midazolam myocardial infarction was detected in one male patient on follow-up examination. One midazolam patient experienced hypotension at the end of the procedure which was reversed by Narcan, and was attributed to the administration of meperidine.

Three midazolam and two diazepam patients had evidence of venous irritation following the study.

Five patients in Dr. White's study (#102), two who received midazolam and three who received diazepam experienced an extended period of drowsiness following the completion of the study. This may have been related to excessive meperidine in individual cases combined with midazolam or diazepam.

Comparable changes in vital signs were observed in all phases of the study.

Summary and Conclusions

In this multicenter study midazolam was used to provide sedation during gastroscopy. It was compared to diazepam when administered intravenously as an adjunct to meperidine, atropine and a topical anesthetic agent.

N 18654

APL

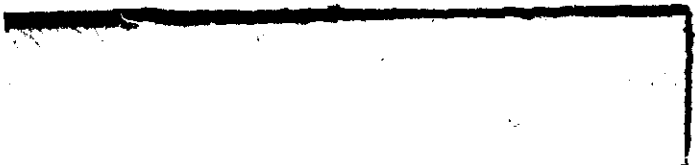
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18-654

DEC 20 1985

Hoffmann-LaRoche
Attention: Karen Church
Nutley, New Jersey 07110

Dear Ms. Church:

Reference is made to your new drug application dated December 15, 1985 submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Versed (midazolam hydrochloride) Injection.

We also acknowledge receipt of your additional communications dated September 4 and November 18, 1985, and additional submissions of the following:

DRAFT package insert dated November 27, 1985,
FINAL immediate container labels dated December 6, 1985, NDA 18-654
DRAFT promotional copy dated December 16, 1985

We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on December 13, 1985. Accordingly, the application is approved, effective on the date of this letter.

The labeling should use "injection" in the title in place of "injectable". Also, the Description section should include the chemical name and graphic formula of the hydrochloride. These changes may be made at the next printing.

Please submit one market package of the drug when available.

You may not legally market the drug until final rulemaking procedures for scheduling under the Controlled Substances Act are enacted by the Drug Enforcement Administration.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80-314.81 for an approved NDA.

Sincerely yours,

Paula Botstein MD

Paula H. Botstein, M.D.
Acting Deputy Director (Medical Affairs)
Office of Drug Research and Review
Center for Drugs and Biologics

N-18654

FP2

ND A 18654

VERSED® (midazolam HCl) INJECTION
Package Insert

Labeling: Shirley Craig
NDA No: 18-654 No. 3-20-87
Reviewed by: David Simpson, M.D.
April 19 87

APPROVED MAY 26 1987

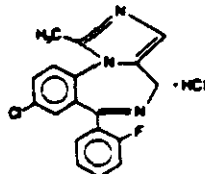
VERSED

brand of
midazolam HCl/Roche
INJECTION

ROCHE

DESCRIPTION: VERSED (brand of midazolam hydrochloride/Roche) is a water-soluble benzodiazepine available as a sterile parenteral dosage form for intravenous or intramuscular injection. Each mL contains midazolam hydrochloride equivalent to 1 mg or 5 mg midazolam compounded with 0.9% sodium chloride and 0.01% disodium edetate, with 1% benzyl alcohol as preservative, the pH is adjusted to approximately 3 with hydrochloric acid and, if necessary, sodium hydroxide.

Midazolam is a white to light yellow crystalline compound, readily soluble in water. The hydrochloride salt of midazolam, which is formed in situ, is soluble in aqueous solutions. Chemically, midazolam HCl is 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine hydrochloride. Midazolam hydrochloride has a calculated molecular weight of 362.25 and the following structural formula:



CLINICAL PHARMACOLOGY: VERSED is a short-acting benzodiazepine central nervous system depressant.

The effects of VERSED on the CNS are dependent on the dose administered, the route of administration, and the presence or absence of other premedications. Onset time of sedative effects after IM administration was 15 minutes, with peak sedation occurring 30 to 60 minutes following injection. In one study, when tested the following day, 73% of the patients who received VERSED intramuscularly had no recall of memory cards shown 30 minutes following drug administration, 40% had no recall of the memory cards shown 60 minutes following drug administration.

Sedation after IV injection was achieved within 3 to 5 minutes; the time of onset is affected by total dose administered and the concurrent administration of narcotic premedication. Seventy-one percent of the patients in the endoscopy studies had no recall of introduction of the endoscope; 62% of the patients had no recall of withdrawal of the endoscope.

When VERSED is given intravenously as an anesthetic induction agent, induction of anesthesia occurs in approximately 1.5 minutes when narcotic premedication has been administered and in 2 to 2.5 minutes without narcotic premedication or with sedative premedication. Some impairment in a level of memory was noted in 90% of the patients studied.

VERSED, used as directed, does not delay awakening from general anesthesia. Gross tests of recovery after awakening (orientation, ability to stand and walk, suitability for discharge from the recovery room, return to baseline finger competency) usually indicate recovery within 2 hours but recovery may take up to 6 hours in some cases. When compared with patients who received thiopental, patients who received midazolam generally recovered at a slightly slower rate. Reaction time under stress (operating automobiles or other hazardous machinery) has not been studied. (See WARNINGS.)

The intravenous administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered.

In patients without intracranial lesions, induction with VERSED is associated with a moderate decrease in cerebrospinal fluid pressure (lumbar puncture measurements), similar to that seen following use of thiopental. Preliminary data in intracranial surgical patients with normal intracranial pressure but decreased compliance (subarachnoid screw measurements) show comparable elevations of intracranial pressure with VERSED and with thiopental during intubation.

Measurements of intraocular pressure in patients without eye disease show a moderate lowering following induction with VERSED; patients with glaucoma have not been studied.

Usual intramuscular premedicating doses of VERSED do not depress the ventilatory response to carbon dioxide stimulation to a clinically significant extent. Induction doses of VERSED depress the ventilatory response to carbon dioxide stimulation for 15 minutes or longer.

more beyond the duration of ventilatory depression following administration of thiopental. Impairment of ventilatory response to carbon dioxide is more marked in patients with chronic obstructive pulmonary disease (COPD). Sedation with intravenous VERSED does not adversely affect the mechanics of respiration (resistance, static, total, and lung volume measurements); total lung capacity and peak expiratory flow decrease significantly but static compliance and maximum expiratory flow at 50% of awake total lung capacity (V_{max}) increase.

In cardiac hemodynamic studies, induction with VERSED was associated with a slight to moderate decrease in mean arterial pressure, cardiac output, stroke volume and systemic vascular resistance. Slow heart rates (less than 65/minute), particularly in patients taking propranolol for angina, tended to rise slightly; faster heart rates (e.g., 85/minute) tended to slow slightly.

The following preliminary pharmacokinetic data for midazolam have been reported. In normal subjects and healthy patients intravenous midazolam exhibited an elimination half-life of 1.2 to 12.3 hours, a large volume of distribution (0.95 to 6.6 L/kg) and a plasma clearance of 0.15 to 0.77 L/h/kg.

Following intravenous administration, less than 0.03% of the dose is excreted in the urine as intact midazolam. Midazolam is rapidly metabolized to 1-hydroxymethyl midazolam, which is conjugated, with subsequent excretion in the urine. Approximately 45% to 57% of the dose is excreted in the urine as the conjugate of 1-hydroxymethyl midazolam, the major metabolite of midazolam. The half-life of excretion of 1-hydroxymethyl midazolam is similar to the parent compound. The concentration of midazolam is 10- to 30-fold greater than that of 1-hydroxymethyl midazolam after single IV administration.

Clinical effects of VERSED do not directly correlate with the blood concentrations of midazolam.

In a small group of patients (n = 11) with congestive heart failure, there appeared to be a 2- to 3-fold increase in the elimination half-life and volume of distribution of midazolam; however, the total body clearance of midazolam appeared to remain unchanged at a single 5-mg intravenous dose. There was no apparent change in the pharmacokinetic profile following the intravenous administration of 5 mg of midazolam to a small group of patients (n = 12) with hepatic dysfunction. There was a 1.5- to 2-fold increase in elimination half-life, total body clearance and volume of distribution in a small group of patients (n = 15) with chronic renal failure.

In a small group (n = 12) of surgical patients, aged 49 to 80 years old, given 0.2 mg/kg midazolam intravenously, there appeared to be a small increase in the volume of distribution and elimination half-life with little change in total body clearance compared to an equal number of younger surgical patients (aged 18 to 30).

The mean absolute bioavailability of midazolam following intramuscular administration is greater than 80%. The mean time of maximum midazolam plasma concentrations following intramuscular dosing occurs within 45 minutes postadministration. Peak concentrations of midazolam as well as 1-hydroxymethyl midazolam after intramuscular administration are about one-half of those achieved after equivalent intravenous doses. The pharmacokinetic profile of elimination after intramuscularly administered midazolam is comparable to that observed following intravenous administration of the drug. Dose-linearity relationships have not been adequately defined.

Midazolam is approximately 87% plasma protein-bound in normal subjects and patients with renal failure. In animals, midazolam has been shown to cross the blood-brain barrier. In animals and in humans, midazolam has been shown to cross the placenta and enter into fetal circulation. It is not known whether midazolam is excreted in human milk.

INDICATIONS: Injectable VERSED is indicated—

- intramuscularly for preoperative sedation (induction of amnesia or drowsiness and relief of apprehension) and to impair memory of perioperative events;
- intravenously as an agent for conscious sedation prior to short diagnostic or endoscopic procedures, such as bronchoscopy, gastroscopy, cystoscopy, coronary angiography and cardiac catheterization, either alone or with a narcotic;

narrows have resulted in increased CNS depression. VERSED is not

VERSED® (brand of

Should hypotension develop, treatment may include administration of midazolam HCl/Neohel

intravenously for induction of general anesthesia, before administration of other anesthetic agents. With the use of narcotic premedication, induction of anesthesia can be obtained with a relatively narrow dose range and in a short period of time. Intravenous VERSED can also be used as a component of intravenous supplementation of nitrous oxide and oxygen (balanced anesthesia) for short surgical procedures. Longer procedures have not been studied.

When used intravenously, VERSED is associated with a high incidence of partial or complete impairment of recall for the next several hours (See CLINICAL PHARMACOLOGY.)

CONTRAINDICATIONS: Injectable VERSED is contraindicated in patients with a known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma. Benzodiazepines may be used in patients with open angle glaucoma only if they are receiving appropriate therapy (See CLINICAL PHARMACOLOGY.)

WARNINGS: VERSED must never be used without individualization of dosage. Prior to the intravenous administration of VERSED in any dose, the immediate availability of oxygen and resuscitative equipment for the maintenance of a patent airway and support of ventilation should be ensured. Patients should be continuously monitored for early signs of under-ventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. Because intravenous VERSED depresses respiration (see CLINICAL PHARMACOLOGY) and because opioid agonists and other sedatives can add to the depression, VERSED should be administered as an induction agent only by a person trained in general anesthesia and should be used in conscious sedation only when a person skilled in maintaining a patent airway and supporting ventilation is present. When used for conscious sedation, VERSED should not be administered by rapid or single bolus intravenous administration. Serious cardiorespiratory adverse events have occurred, predominantly in older chronically ill patients and/or with concomitant use of other cardiorespiratory depressant agents. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death.

Injectable VERSED should not be administered to patients in shock or coma, or in acute alcohol intoxication with depression of vital signs.

The hazards of intra-arterial injection of VERSED solutions in humans are unknown; therefore, extreme precautions against unintended intra-arterial injection should be taken. Extravasation should also be avoided.

Higher risk surgical patients or debilitated patients require lower dosages for induction of anesthesia, whether premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure have a 1.5- to 2-fold increase in elimination half-life, total body clearance and volume of distribution of midazolam. Patients with congestive heart failure have a 2- to 3-fold increase in the elimination half-life and volume of distribution of midazolam. Patients over the age of 55 years require lower dosages for induction of anesthesia, whether premedicated or not. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduced initial dosage of VERSED is recommended and the possibility of profound and/or prolonged effect should be considered.

Concomitant use of barbiturates, alcohol or other central nervous system depressants may increase the risk of under-ventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with a narcotic.

The decision as to when patients who have received injectable VERSED, particularly on an outpatient basis, may again engage in activities requiring complete mental alertness, operate hazardous machinery or drive a motor vehicle must be individualized. Gross tests of recovery from the effects of VERSED (see CLINICAL PHARMACOLOGY) cannot be relied upon alone to predict reaction time under stress. This drug is never used alone during anesthesia and the contribution of other anesthetic drugs and events can vary. It is recommended that no patient operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia and surgery, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepine drugs (diazepam and chloridiazepoxide) has been suggested in several studies. If this drug is used during pregnancy, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS: General: Because an increase in cough reflex and laryngospasm may occur with peroral endoscopic procedures, the use of a topical anesthetic agent and the availability of necessary countermeasures are recommended. The use of narcotic premedication is recommended for bronchoscopies.

intravenous doses of VERSED should be decreased by about 30% for elderly and debilitated patients (See WARNINGS and DOSAGE AND ADMINISTRATION.) These patients will also probably take longer to recover completely after VERSED administration to the induction of anesthesia.

VERSED does not protect against the increase in intracranial pressure or circulatory effects noted following administration of succinylcholine.

VERSED does not protect against the increase in intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: To assure safe and effective use of benzodiazepines, the following information and instructions should be communicated to the patient when appropriate:

1. Inform your physician about any alcohol consumption and medicine you are now taking, including drugs you buy without a prescription. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol during benzodiazepine treatment.
2. Inform your physician if you are pregnant or are planning to become pregnant.
3. Inform your physician if you are nursing.

Drug Interactions: The hypnotic effect of intravenous VERSED is accentuated by premedication, particularly narcotics (e.g., morphine, meperidine and fentanyl) and also scopolamine and butorphanol (fentanyl and droperidol). Consequently, the dosage of VERSED should be adjusted according to the type and amount of premedication administered (See DOSAGE AND ADMINISTRATION.)

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of intramuscular VERSED for premedication.

The use of VERSED as an induction agent may result in a reduction of the inhalation anesthetic requirement during maintenance of anesthesia (See CLINICAL PHARMACOLOGY.)

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium and does not protect against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single inducing dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydralazine, 6-aminocaproic acid, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, bupivacaine HCl and Cetacaine) have been observed.

Drug laboratory test interactions: Midazolam has not been shown to interfere with results obtained in clinical laboratory tests.

Carcinogenesis, mutagenesis, impairment of fertility:

Carcinogenesis: Midazolam maleate was administered with diet in mice and rats for two years at dosages of 1, 3 and 10 mg/kg/day. In female mice in the highest dose group there was a marked increase in the incidence of hepatic tumors. In high dose male rats there was a small but statistically significant increase in benign thyroid follicular cell tumors. Dosages of 9 mg/kg/day of midazolam maleate (25 times a human dose of 0.35 mg/kg) do not increase the incidence of tumors. The pathogenesis of induction of these tumors is not known. These tumors were found after chronic administration, whereas human use will ordinarily be of single or several doses.

Mutagenesis: Midazolam did not have mutagenic activity in *Salmonella typhimurium* (5 bacterial strains), Chinese hamster lung cells (V79), human lymphocytes, or in the micronucleus test in mice.

Impairment of fertility: A reproduction study in male and female rats did not show any impairment of fertility at dosages up to ten times the human IV dose of 0.35 mg/kg.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section.

Segment II teratology studies, performed with midazolam maleate injectable in rabbits and rats at 5 and 10 times the human dose of 0.35 mg/kg, did not show evidence of teratogenicity.

Nonteratogenic effects: Studies in rats showed no adverse effects on reproductive parameters during gestation and lactation. Dosages tested were approximately 10 times the human dose of 0.35 mg/kg.

Labor and delivery: In humans, measurable levels of midazolam were found in maternal venous serum, umbilical venous and arterial serum and amniotic fluid, indicating placental transfer of the drug. Following intramuscular administration of 0.05 mg/kg of midazolam, both the venous and the umbilical arterial serum concentrations were lower than maternal concentrations.

The use of injectable VERSED in obstetrics has not been evaluated or clinical studies. Because midazolam is transferred transplacentally

may have resulted in reduced CNS depression. VERSED is not recommended for electrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness of VERSED in children below the age of 18 have not been established.

ADVERSE REACTIONS: Fluctuations in vital signs were the most frequently seen findings following parenteral administration of VERSED and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate. Serious cardiorespiratory adverse events have also occurred. (See WARNINGS.)

In the conscious sedation studies, hypotension occurred more frequently after IV administration of VERSED in patients concurrently premedicated with morphine. It should especially be noted that VERSED does not modify the circulatory effects of neuromuscular blocking agents or the tachycardia and blood pressure rises seen during endotracheal intubation under light general anesthesia. During the clinical investigations, three cases (0.2%) of transient fall in blood pressure greater than 50% were reported during the induction phase.

Reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity and combatsiveness have been reported. (See DOSAGE AND ADMINISTRATION.)

The following adverse reactions were reported after intramuscular administration:

headache (1.3%)	Local effects at IM injection site
	pain (3.7%)
	induration (0.5%)
	redness (0.5%)
	muscle stiffness (0.3%)

The following adverse reactions were reported subsequent to intravenous administration:

hiccuping (3.8%)	Local effects at the IV site
nausea (2.8%)	tenderness (5.6%)
vomiting (2.6%)	pain during injection (5.0%)
coughing (1.3%)	redness (2.8%)
"oversedation" (1.6%)	induration (1.7%)
headache (1.5%)	phlebitis (0.4%)
drowsiness (1.2%)	

Other adverse experiences, observed mainly following IV injection and occurring at an incidence of less than 1.0%, are as follows:

Respiratory: Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea.

Cardiovascular: Bigeminy, premature ventricular contractions, ventricular episode, tachycardia, nodal rhythm.

Gastrointestinal: Acid taste, excessive salivation, retching.

CNS/Neuromuscular: Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbances, insomnia, nightmares, atetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphoria, paresthesia.

Special sense: Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, light-headedness.

Integumentary: Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus.

Miscellaneous: Yawning, lethargy, chills, weakness, toothache, "mint" feeling, hematoma.

DRUG ABUSE AND DEPENDENCE: Midazolam is subject to Schedule IV control under the Controlled Substances Act of 1970.

Midazolam was actively self-administered in primate models used to assess the positive reinforcing effects of psychoactive drugs.

Midazolam produced physical dependence of a mild to moderate intensity in cynomolgus monkeys after 5 to 10 weeks of administration. Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

OVERDOSEAGE: While there is insufficient human data on overdose with VERSED, the manifestations of VERSED overdose are expected to be similar to those observed with other benzodiazepines and include sedation, ataxia, confusion, impaired coordination, diminished reflexes, coma and untoward effects on vital signs. No evidence of specific organ toxicity from VERSED overdose would be expected.

Treatment of overdose: Treatment of injectable VERSED overdose is the same as that followed for overdose with other benzodiazepines. Respiration, pulse rate and blood pressure should be monitored and general supportive measures should be employed. Attention should be given to the maintenance of a patent airway and

should hypoxemia be avoided. Treatments may include mechanical ventilation, respiratory support, judicious use of vasopressors appropriate to the clinical situation, if indicated, and other appropriate supportive measures. There is no information as to whether paracetamol, salicylates, local anesthetics or his toxicology are of any value in the treatment of midazolam overdose.

DOSAGE AND ADMINISTRATION: Dosage should be individualized. In general, lower doses are required in elderly or debilitated patients. The dosage of intravenous VERSED administered should be adjusted according to the type and amount of premedication used. Excessive doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest, especially in elderly or debilitated patients. (See WARNINGS.) When intravenous use is indicated, oxygen, resuscitative equipment and personnel resources for the maintenance of a patent airway should be immediately available. (See WARNINGS.)

Reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity and combatsiveness have been reported. These reactions may be due to inadequate or excessive dosing or improper administration of VERSED, however, consideration should be given to the possibility of cerebral hypoxia or true paradoxical reactions. Should such reactions occur, caution should be exercised before continuing administration of VERSED.

Injectable VERSED may be mixed in the same syringe with the following frequently used premedications: morphine sulfate, meperidine, atropine sulfate or scopolamine. Injectable VERSED is compatible with 5% dextrose in water, 0.9% sodium chloride and lactated Ringer's solution.

For intramuscular use, VERSED should be injected deep in a large muscle mass. Intravenous VERSED for conscious sedation should be administered slowly; rapid injection may cause respiratory depression or apnea requiring assisted or controlled ventilation. For induction of general anesthesia, the usual dose should be administered over 20 to 30 seconds for optimum effect. Extreme care should be taken to avoid intra-arterial injection or extravasation (see WARNINGS).

INTRAMUSCULAR:

For preoperative sedation (reduction of sleepiness or drowsiness and relief of apprehension) and to improve memory of perioperative events.

USUAL ADULT DOSE

For premedication the recommended dose of VERSED is 0.07 to 0.08 mg/kg IM (approximately 5 mg IM for an average adult) approximately one hour before surgery. Onset is within 15 minutes, peaking at 30 to 60 minutes. It can be administered concurrently with atropine sulfate or scopolamine hydrochloride and reduced doses of narcotics.

INTRAVENOUSLY

Endoscopic or Cardiovascular Procedures:

For conscious sedation, VERSED can be used either alone or together with a narcotic immediately before the procedure, with supplemental doses of VERSED to maintain the desired level of sedation throughout the procedure. For peroral procedures, the use of an appropriate topical anesthetic is recommended. For bronchoscopic procedures, the use of narcotic premedication is recommended.

When used for conscious sedation, VERSED should not be administered by rapid or single bolus intravenous administration. (See WARNINGS.) VERSED should be administered immediately prior to the procedure.

Initial Dose:
An initial titration with a small dose, such as 2 to 2.5 mg (0.035 mg/kg), administered over a 2 to 3 minute period, is suggested for an average healthy adult, and approximately 1 to 1.5 mg for older or chronically ill or debilitated patients. After waiting 1 to 2 minutes, if further sedative effect is necessary the dosage may then be further titrated in small increments of the initial dose to the desired effect, i.e., the initiation of slurred speech. For ease of titration, VERSED 1 mg/mL formulation is recommended. In addition, both the 5 mg/mL and 1 mg/mL formulations of VERSED may be diluted with 0.9% sodium chloride or 5% dextrose in water.

Total Dose:
Generally, a total dose of up to 0.1 mg/kg is adequate in average healthy adults. However, in titrating the dose to individual needs, a lower dose may suffice. Total dosage should be altered by about 30% in the elderly and debilitated and in patients with limited pulmonary reserve. Narcotic premedication results in less variability in patient response. If narcotic premedication or other CNS depressants are used, lower dosage by 25% to 30% is

continued on next page

INTRAVENOUSLY (cont.)

USUAL ADULT DOSEAGE (cont.)

healthy patients, and by a rate of 10% to 50% in patients who are age 60 years or older or debilitated. Because the danger of underventilation or apnea is greatest in elderly patients and those with chronic disease states, and because peak effect may take longer in these patients, increments should be smaller and the rate of injection slower.

Maintenance Dose

Additional maintenance doses may be given in increments of 25% of the initial dose to maintain the desired level of sedation.

Individual response to the drug is variable, particularly when a narcotic premedication is not used. The dosage should be titrated to the desired effect according to the patient's age and clinical status.

Unpremedicated Patients:

In the absence of premedication, an average adult under the age of 55 years will usually require an initial dose of 0.3 to 1.36 mg/kg for induction, administered over 20 to 30 seconds and allowing 2 minutes for effect. If needed to complete induction, increments of approximately 25% of the patient's initial dose may be used; induction may instead be completed with volatile liquid inhalational anesthetics. In resistant cases, up to 0.8 mg/kg total dose may be used for induction, but such larger doses may prolong recovery.

Unpremedicated patients over the age of 55 years usually require less VERSED for induction; an initial dose of 0.3 mg/kg is recommended. Unpremedicated patients with severe systemic disease or other debilitation usually require less VERSED for induction. An initial dose of 0.2 to 0.25 mg/kg will usually suffice; in some cases, as little as 0.15 mg/kg may suffice.

Premedicated Patients:

When the patient has received sedative or narcotic premedication, particularly narcotic premedication, the rate of recommended doses is 0.15 to 0.2 mg/kg.

In average adults below the age of 55 years, a dose of 0.25 mg/kg, adminis-

continued

tered over 20 to 30 seconds and allowing 2 minutes for effect, will usually suffice.

The initial dose of 0.2 mg/kg is recommended for good risk (ASA I & II), surgical patients over the age of 55 years.

In some patients with severe systemic disease or debilitation, as little as 0.15 mg/kg may suffice.

Narcotic premedication frequently used during clinical trials included tertiary (1.5 to 2 mg/kg *BC*, administered five minutes before induction), morphine (dosage individualized, up to 0.35 mg/kg *BC*), meperidine (dosage individualized, up to 1 mg/kg *BC*) and hyaluronidase (0.52 mL/kg *BC*). Sedative premedications were hydroxyzine pamoate (100 mg orally) and sodium secobarbital (200 mg orally). Except for intravenous tertiary, administered five minutes before induction, all other premedications should be administered approximately one hour prior to the time anticipated for VERSED induction.

Incremental fractions of approximately 25% of the induction dose should be given in response to signs of lightening of anesthesia and repeated as necessary.

Injectable VERSED can also be used during maintenance of anesthesia, for short surgical procedures, as a component of balanced anesthesia. Effective narcotic premedication is especially recommended in such cases. Long surgical procedures have not been studied.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED: Package configurations containing midazolam hydrochloride equivalent to 5 mg midazolam/mL:

- 1-mL vials (5 mg)—boxes of 10 (NDC 0004-1974-01);
- 2-mL vials (10 mg)—boxes of 10 (NDC 0004-1973-01);
- 5-mL vials (25 mg)—boxes of 10 (NDC 0004-1975-01);
- 10-mL vials (50 mg)—boxes of 10 (NDC 0004-1948-01);
- 2-mL, *Tal-E-Ject*® disposable syringes (10 mg)—boxes of 10 (NDC 0004-1947-01).

Package configurations containing midazolam hydrochloride equivalent to 1 mg midazolam/mL:

- 2-mL vials (2 mg)—boxes of 10 (NDC 0004-1968-08);
- 5-mL vials (5 mg)—boxes of 10 (NDC 0004-1969-08);
- 10-mL vials (10 mg)—boxes of 10 (NDC 0004-2000-08).

THIS PACKAGE INSERT ISSUED MARCH 1987.

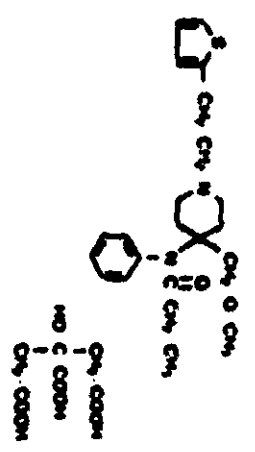
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ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Printed in U.S.A.

SUFENTA[®] SUFENTANIL CITRATE) INJECTION

PACKAGE INSERT A



Bufentanil citrate is a potent analgesic, approximately 100 times more potent than morphine. It is a Schedule II controlled substance. The chemical formula is C₂₃H₃₅N₃O₇.

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INDICATIONS AND USAGE
SUFENTA is indicated for the management of moderate to severe pain in patients who are opioid tolerant. It is not recommended for use in patients who are not opioid tolerant. The use of SUFENTA in patients who are not opioid tolerant may result in respiratory depression, coma, and death. The use of SUFENTA in patients who are not opioid tolerant may result in respiratory depression, coma, and death.

CONTRAINDICATIONS
SUFENTA is contraindicated in patients with known hypersensitivity to the drug or any of its components. It is also contraindicated in patients with acute or severe bronchial asthma, acute or severe asthma, or severe chronic obstructive pulmonary disease. It is also contraindicated in patients with acute or severe asthma, or severe chronic obstructive pulmonary disease.

WARNINGS
SUFENTA is a potent analgesic, approximately 100 times more potent than morphine. It is a Schedule II controlled substance. The use of SUFENTA in patients who are not opioid tolerant may result in respiratory depression, coma, and death. The use of SUFENTA in patients who are not opioid tolerant may result in respiratory depression, coma, and death.

PRECAUTIONS
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ADVERSE REACTIONS
SUFENTA is a potent analgesic, approximately 100 times more potent than morphine. It is a Schedule II controlled substance. The use of SUFENTA in patients who are not opioid tolerant may result in respiratory depression, coma, and death. The use of SUFENTA in patients who are not opioid tolerant may result in respiratory depression, coma, and death.

HOW SUPPLIED
SUFENTA is available in the following strengths: 0.5 mg/mL, 1 mg/mL, 2 mg/mL, 5 mg/mL, and 10 mg/mL. Each mL contains 0.5 mg, 1 mg, 2 mg, 5 mg, or 10 mg of SUFentanil Citrate, respectively. Each mL also contains 0.5 mg, 1 mg, 2 mg, 5 mg, or 10 mg of Citric Acid, respectively.

HOW SUPPLIED
SUFENTA is available in the following strengths: 0.5 mg/mL, 1 mg/mL, 2 mg/mL, 5 mg/mL, and 10 mg/mL. Each mL contains 0.5 mg, 1 mg, 2 mg, 5 mg, or 10 mg of SUFentanil Citrate, respectively. Each mL also contains 0.5 mg, 1 mg, 2 mg, 5 mg, or 10 mg of Citric Acid, respectively.

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NDA 18-654

NOV 8 1985

Hoffmann-La Roche
Attention: Karen K. Church
Nutley, New Jersey 07110

Dear Ms. Church:

Please refer to your new drug application dated December 15, 1982 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation Midazolam Injectable.

We also acknowledge receipt of your additional communications dated May 2, June 7, September 20, 1983 (two submissions); March 1, April 23, May 10, October 8, and November 14, 1984; April 12, May 17, May 28, July 26, and August 16, 1985.

We have completed the review of this application as submitted with draft labeling. However, before the application may be approved, it will be necessary for you (1) to submit final printed labeling exactly as stated below and (2) to agree to correct certain deficiencies in the biopharmaceutics/pharmacokinetics portion of the application. Note that several specific requests for additional material in the labeling will be found in the text below set between brackets [].

I. LABELING:

DESCRIPTION: VERSED (midazolam hydrochloride) is a water soluble benzodiazepine available as a sterile parenteral dosage form for intravenous or intramuscular injection. Each ml contains midazolam hydrochloride equivalent to 5 mg midazolam compounded with 0.8% sodium chloride and 0.01% disodium edetate, with 1% benzyl alcohol as preservative; the pH is adjusted to approximately 3 with hydrochloric acid and, if necessary, sodium hydroxide.

Chemically, midazolam is 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine. It is a white to light yellow crystalline compound, insoluble in water; the hydrochloride salt is soluble in aqueous solutions. Midazolam has a calculated molecular weight of 325.78 and the following structural formula:

[Place structural formula here.]

CLINICAL PHARMACOLOGY: VERSED is a short-acting benzodiazepine central nervous system depressant.

The effects of VERSED on the CNS are dependent on the dose administered, the route of administration, and the presence or absence of other premedications. Onset time of sedative effects after IM administration was 15 minutes, with peak sedation occurring 30 to 60 minutes following injection. In one study midazolam produced impaired recall or recognition in a memory test in about half of the patients tested.

Sedation after IV injection was achieved more rapidly i.e., within 3 to 5 minutes; the time of onset is affected by total dose administered and the concurrent administration of narcotic premedication.

When VERSED is given intravenously as an anesthetic induction agent, induction of anesthesia occurs in approximately 1.5 minutes when narcotic premedication has been administered and in 2 to 2.5 minutes without narcotic premedication or with sedative premedication. Some impairment in a test of memory was noted in 90% of the patients studied.

The intravenous administration of midazolam decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of midazolam administered.

In patients without intracranial lesions, induction with midazolam is associated with a moderate decrease in cerebrospinal fluid pressure (lumbar puncture measurements) similar to that seen following use of thiopental. Preliminary data in intracranial surgery patients with normal intracranial pressure but decreased compliance (subarachnoid screw measurements) show a moderate lowering of intracranial pressure following induction with midazolam.

Measurements of intraocular pressure in patients without eye disease show a moderate lowering following induction with midazolam; patients with glaucoma have not been studied.

VERSED, used as directed, does not delay awakening from general anesthesia. Gross tests of recovery after awakening (orientation, ability to stand and walk, suitability for discharge from the recovery room, return to baseline Treiger competency) usually indicate recovery within 2 hours but recovery may take up to 6 hours in some cases. When compared to patients who received thiopental, patient who received midazolam generally recovered at a slightly slower rate. Reaction time under stress (operating automobiles or other hazardous machinery) has not been studied (See WARNINGS).

Usual intramuscular premedicating doses of midazolam do not depress the ventilatory response to carbon dioxide stimulation to a clinically significant extent. Induction doses greatly depress the ventilatory response to carbon dioxide stimulation for more than 15 minutes or longer than thiopental. Impairment of ventilatory response to carbon dioxide is more marked in patients with chronic obstructive pulmonary disease (COPD). Sedation with

intravenous midazolam does not adversely affect the mechanics of respiration (resistance, static recoil, most lung volume measurements); total lung capacity and peak expiratory flow decrease significantly but static compliance and maximum expiratory flow at 50% of awake total lung capacity (V_{max}) increase.

In cardiac hemodynamic studies, induction with midazolam was associated with a slight to moderate decrease in mean arterial pressure, cardiac output, stroke volume and systemic vascular resistance. Slow heart rates (less than 65/minute), particularly in patients taking propranolol for angina, tended to rise slightly; faster heart rates (e.g., 85/minute) tended to slow slightly.

The following preliminary pharmacokinetic data for midazolam has been reported. In normal subjects and healthy patients intravenous midazolam exhibited an elimination half-life of 1.2-12.3 hours, a large volume of distribution (0.95 to 6.6 L/kg) and a plasma clearance of 0.15 to 0.77 L/hr/kg.

Following intravenous administration, less than 0.03% of the dose is excreted in the urine as intact midazolam. Midazolam is rapidly metabolized to 1-hydroxymethyl midazolam which is conjugated with subsequent excretion in the urine. Approximately 45% to 57% of the dose is excreted in the urine as the conjugate of 1-hydroxymethyl midazolam, the major metabolite of midazolam. The half-life of elimination of 1-hydroxymethyl midazolam is similar to the parent compound. The concentration of midazolam is 10- to 30-fold greater than that of 1-hydroxymethyl midazolam after single IV administration.

In a small group of patients (n=11) with congestive heart failure, there appeared to be a 2- to 3-fold increase in the elimination half-life and volume of distribution of VERSED; however, the total body clearance of VERSED appeared to remain unchanged at a single 5 mg intravenous dose. There was no apparent change in the pharmacokinetic profile following the intravenous administration of 5 mg of VERSED to a small group of patients (n=12) with hepatic dysfunction. There was a 1.5- to 2-fold increase in elimination half-life, total body clearance and volume of distribution in a small group of patients (n=15) with chronic renal failure. In a small group (n=12) of surgical patients, aged 49-60 years old, given 0.2 mg/kg VERSED intravenously there appeared to be a small increase in the volume of distribution and elimination half life with little change in total body clearance compared to an equal number of younger surgical patients (aged 18-30).

The mean absolute bioavailability of VERSED following intramuscular administration is greater than 90%. The mean time of maximum VERSED plasma concentrations following intramuscular dosing occurs within 45 minutes post-administration. Peak concentrations of midazolam as well as 1-hydroxymethyl midazolam after intramuscular administration are about one-half of those achieved after equivalent intravenous doses. The pharmacokinetic profile of elimination after intramuscularly administered VERSED is comparable to that observed following intravenous administration of the drug. Dose-linearity relationships have not been adequately defined.

Midazolam is approximately 97% plasma protein-bound in normal subjects and patients with renal failure. In animals, VERSED has been shown to cross the blood brain barrier. In animals and in humans, VERSED has been shown to cross the placenta and enter into fetal circulation. It is not known whether VERSED is excreted in human milk.

INDICATIONS: Injectable VERSED is indicated --

intramuscularly for preoperative sedation (induction of sleepiness or drowsiness and relief of apprehension) and to impair memory of peri-operative events.

intravenously as an agent for conscious sedation prior to short diagnostic or endoscopic procedures, such as bronchoscopy, gastroscopy, cystoscopy, coronary angiography and cardiac catheterization, either alone or with a narcotic;

intravenously for induction of general anesthesia, before administration of other anesthetic agents. With the use of narcotic premedication, induction of anesthesia can be attained within a relatively narrow dose range and in a short period of time. Intravenous VERSED can also be used as a component of intravenous supplementation of nitrous oxide and oxygen (balanced anesthesia) for short surgical procedures; longer procedures have not been studied. When used intravenously, VERSED is associated with a high incidence of partial or complete impairment of recall for the next several hours, (see CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS: Injectable VERSED is contraindicated in patients with a known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma. Benzodiazepines may be used in patients with open angle glaucoma only if they are receiving appropriate therapy (see also CLINICAL PHARMACOLOGY).

WARNINGS: PRIOR TO THE INTRAVENOUS ADMINISTRATION OF MIDAZOLAM IN ANY DOSE, THE IMMEDIATE AVAILABILITY OF OXYGEN AND RESUSCITATIVE EQUIPMENT FOR THE MAINTENANCE OF A PATENT AIRWAY AND SUPPORT OF VENTILATION SHOULD BE INSURED. Because intravenous VERSED depresses respiration (see Clinical Pharmacology) and because opioid agonist and other sedatives can add to this depression, VERSED should be administered as an induction agent only by a person trained in general anesthesia and should be used in conscious sedation only when a person skilled in maintaining a patent airway and supporting ventilation is present.

Injectable VERSED should not be administered to patients in shock or coma, or in acute alcohol intoxication with depression of vital signs.

The hazards of intra-arterial injection of VERSED solutions in humans are unknown, therefore, extreme precautions against unintended intra-arterial injection should be taken. The following have been observed following injection in the _____ artery of the _____ (species) _____.

[Note: Please supply data, if available.]

Extravasation should also be avoided.

Higher risk surgical patients or debilitated patients require less VERSED for induction of anesthesia, whether premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure have a 1.5-2 fold increase in elimination half-life, total body clearance and volume of distribution of VERSED. Patients with congestive heart failure have a 2-3 fold increase in the elimination half-life and volume of distribution of VERSED. Patients over the age of 55 years require less VERSED for induction of anesthesia, whether premedicated or not. Since elderly patients frequently have inefficient function of one or more organ systems, and since dosage has been shown to decrease with age, reduced initial dosage of VERSED is recommended and the possibility of profound and/or prolonged effect should be considered.

Concomitant use of barbiturates, alcohol or other central nervous system depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with a narcotic.

The decision as to when patients who received injectable VERSED, particularly on an outpatient basis, may again engage in occupations requiring complete mental alertness, operate hazardous machinery or drive a motor vehicle must be individualized. Gross tests of recovery from the effects of VERSED (see CLINICAL PHARMACOLOGY) cannot be relied on alone to predict reaction time under stress. This drug is never used alone during anesthesia and the contribution of other peri-operative drugs and events can vary. It is recommended that no patient operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia and surgery, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepine drugs (diazepam and chlordiazepoxide) has been suggested in several studies. If this drug is used during pregnancy, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS: General: Since an increase in cough reflex and laryngospasm may occur with per oral endoscopic procedures, the use of a topical anesthetic agent and the availability of necessary counter measures are recommended. The use of narcotic premedication is recommended for bronchoscopies.

Intravenous doses of VERSED should be decreased by 25% to 30% for elderly and debilitated patients (See WARNINGS & DOSAGE AND ADMINISTRATION). These patients will also probably take longer to recover completely after VERSED administration for the induction of anesthesia.

Midazolam does not protect against the increase in intracranial pressure or circulatory effects noted following administration of succinylcholine.

Midazolam does not protect against the increase in intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: To assure safe and effective use of benzodiazepines, the following information and instructions should be given to the patient when appropriate:

1. Inform your physician about any alcohol consumption and medicine you are now taking, including drugs you buy without a prescription. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol during benzodiazepine treatment.
2. Inform your physician if you are pregnant or are planning to become pregnant.
3. Inform your physician if you are nursing.

Drug interactions: The hypnotic effect of intravenous VERSED is accentuated by premedication, particularly narcotics (e.g., morphine, meperidine and fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, the dosage of VERSED should be adjusted according to the type and amount of premedication administered. (See DOSAGE AND ADMINISTRATION.)

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of intramuscular VERSED for premedication.

The use of VERSED as an induction agent may result in a reduction of the inhalation anesthetic requirement during maintenance of anesthesia (see CLINICAL PHARMACOLOGY).

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. Midazolam does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium and does not protect against

the increased intracranial pressure noted following administration of succinylcholine. Midazolam does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with results obtained in clinical laboratory tests.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:

Carcinogenesis: Midazolam maleate was administered with diet in mice and rats for two years at dosages up to 80 mg/kg/day. In female mice in the highest dose group there was a marked increase in the incidence of hepatic tumors. In high dose male rats there was a small but statistically significant increase in benign thyroid follicular cell tumors. The pathogenesis of induction of these tumors is not known. These tumors were found after chronic administration, whereas human use will ordinarily be of single or several doses.

Mutagenesis: Midazolam did not have mutagenic activity in *Salmonella typhimurium* (5 bacterial strains), Chinese hamster lung cells (V79), human lymphocytes, or in the micronucleus test in mice.

Impairment of fertility: A reproduction study in male and female rats did not show any impairment of fertility at dosages up to ten times the human IV dose of 0.35 mg/kg.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section.

Segment II teratology studies performed with midazolam maleate injectable in rabbits and rats at 5 and 10 times the human dose of 0.35 mg/kg, did not show evidence of teratogenicity.

Nonteratogenic effects: Studies in rats showed no adverse effects on reproductive parameters during gestation and lactation. Dosages tested were approximately 10 times the human dose of 0.35 mg/kg.

Labor and delivery: In humans, measurable levels of VERSED were found in maternal venous serum, umbilical venous and arterial serum and amniotic fluid, indicating placental transfer of the drug. Following intramuscular administration of 0.05 mg/kg of VERSED, both the venous and the umbilical arterial serum concentrations were lower than maternal concentrations.

The use of injectable VERSED in obstetrics has not been evaluated in clinical studies. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, midazolam is not recommended for obstetrical use.

Nursing mothers: It is not known whether VERSED is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness of VERSED in children below the age of 18 have not been established.

ADVERSE REACTIONS: Fluctuations in vital signs were the most frequently seen findings following parenteral administration of VERSED and included decreased tidal volume and/or respiratory rate decrease (25.2% of patients following IV and 11.0% of patients following IM administration) and apnea (16.8% of patients following IV administration), as well as variations in blood pressure and pulse rate. These are common occurrences during anesthesia and surgery and are affected by the lightening or deepening of anesthesia, instrumentation, intubation and use of concomitant drugs.

In the conscious sedation studies, hypotension occurred more frequently after IV administration of VERSED in patients concurrently premedicated with meperidine. It should especially be noted that VERSED does not modify the circulatory effects of neuromuscular blocking agents or the tachycardia and blood pressure rises seen during endotracheal intubation under light general anesthesia. Three cases (___%) of transient blood pressure fall greater than 50% were reported around the time of induction during clinical investigation.

[Note: Please provide percentage above.]

The following rates of adverse reactions were reported after intramuscular administration:

headache (1.3%)	<u>Local effects at IM injection site</u>
	pain (3.7%)
	induration (0.5%)
	redness (0.5%)
	muscle stiffness (0.3%)

The following adverse reactions were reported subsequent to intravenous administration:

hiccoughs (4.2%)	<u>Local effects at the IV site</u>
nausea (2.7%)	tenderness (5.9%)
vomiting (2.5%)	pain during injection (5.4%)
coughing (1.4%)	redness (2.8%)
"overseation" (1.4%)	induration (1.8%)
headache (1.3%)	phlebitis (0.4%)
drowsiness (1.0%)	

Other adverse experiences, observed mainly following IV injection and occurring at a rate of less than 1.0% are as follows:

Respiratory: Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea.

Cardiovascular: Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm.

Gastrointestinal: Acid taste, excessive salivation, retching.

CNS/Neuromuscular: Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, agitation, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, tonic/clonic movements, muscle tremor, involuntary movements, athetoid movements, dizziness, dyspnea, slurred speech.

Ophthalmic: Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids.

Integumentary: Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site.

Miscellaneous: Yawning, lethargy, chills, weakness, toothache, hematoma.

DRUG ABUSE AND DEPENDENCE: Midazolam is subject to Schedule IV control under the Controlled Substances Act of 1970.

Midazolam was actively self-administered in primate models used to assess the positive reinforcing effects of psychoactive drugs.

Midazolam produced physical dependence of a mild to moderate intensity in cynomolgus monkeys after 5 to 10 weeks of administration. Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

OVERDOSAGE: There have been no reports of injectable VERSED overdosage. The manifestations of VERSED overdosage are expected to be similar to those observed with other benzodiazepines and include sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma and untoward effects on vital signs. No evidence of specific organ toxicity from VERSED overdosage would be expected.

Treatment of overdosage: Treatment of injectable VERSED overdosage is the same as that followed for overdosage with other benzodiazepines. Respiration, pulse rate and blood pressure should be monitored and general supportive

measures should be employed. Attention should be given to the maintenance of a patent airway and support of ventilation. An intravenous infusion should be started. Should hypotension develop, treatment may include intravenous fluid therapy, repositioning, judicious use of vasopressors appropriate to the clinical situation, if indicated, and other appropriate countermeasures. There is no information as to whether peritoneal dialysis, forced diuresis or hemodialysis are of any value in the treatment of VERSED overdose.

DOSE AND ADMINISTRATION: Dosage should be individualized. Lower doses are required in elderly or debilitated patients. The dosage of intravenous VERSED administered should be adjusted according to the type and amount of premedication used. When intravenous use is indicated, oxygen, resuscitative equipment and personnel resources for the maintenance of a patent airway should be immediately available. (See WARNINGS section.)

Injectable VERSED may be mixed in the same syringe with the following frequently used premedications: morphine sulfate, meperidine, atropine sulfate or scopolamine. Injectable VERSED is compatible with 5% dextrose in water, 0.9% sodium chloride, and lactated Ringer's solution.

For intramuscular use, VERSED should be injected deep in a large muscle mass. Intravenous VERSED for endoscopy should be administered slowly; rapid injection may cause respiratory depression or apnea requiring assisted or controlled ventilation. For induction of general anesthesia, the initial dose should be administered over 20-30 seconds for optimum effect. Extreme care should be taken to avoid intra-arterial injection or extravasation (see WARNINGS).

INTRAMUSCULARLY

For preoperative sedation (induction of sleepiness or drowsiness and relief of apprehension) and to impair memory of peri-operative events.

USUAL ADULT DOSE

For premedication the recommended dose of VERSED is 0.07 to 0.08 mg/kg IM (approximately 5 mg IM for an average adult) approximately one hour before surgery. Onset is within 15 minutes, peaking at 30-60 minutes. It can be administered concomitantly with atropine sulfate or scopolamine hydrochloride and reduced doses of narcotics.

INTRAVENOUSLY
Endoscopic or Cardiovascular
Procedures

For conscious sedation, VERSED can be used either alone or together with a narcotic immediately before the procedure with supplemental doses of VERSED to maintain the desired level of sedation throughout the procedure. For per oral procedures, the use of an appropriate topical anesthetic is recommended. For bronchoscopic procedures, the use of narcotic premedication is recommended.

Induction of Anesthesia

For induction of general anesthesia, before administration of other anesthetic agents.

Titrate dosage to desired sedative end point, e.g., slurring of speech, with slow administration immediately prior to the procedure. Generally 0.1 to 0.15 mg/kg is adequate, but up to 0.2 mg/kg may be given, particularly when concomitant narcotics are omitted. Additional maintenance doses may be given in increments of 25% of the initial dose to maintain the desired level of sedation. Narcotic premedication results in less variability in patient response. Dosage should be lowered by about 25% to 30% if narcotic premedication is used. Patients 60 years or older may require doses lower by about 30% than younger patients.

Unpremedicated Patients

In the absence of premedication, an average adult under the age of 55 years will usually require an initial dose of 0.3-0.35 mg/kg for induction, administered over 20-30 seconds and allowing 2 minutes for effect. If needed to complete induction, increments of approximately 25% of the initial or recommended dose may be used; induction may instead be completed with volatile liquid inhalational anesthetics. In resistant cases, up to 0.6 mg/kg total VERSED may be used for induction, but such larger doses may prolong recovery.

Unpremedicated patients over the age of 55 years usually require less VERSED for induction; an initial dose of 0.3 mg/kg is recommended. Unpremedicated patients with severe systemic disease or other debilitation usually require less VERSED for induction. An initial dose of 0.2-0.25 mg/kg will usually suffice; in some cases, as little as 0.15 mg/kg may suffice.

Premedicated Patients

When the patient has received satisfactory sedative or narcotic premedication, particularly narcotic premedication, the range of recommended doses is 0.15-0.35 mg/kg.

In average adults below the age of 55 years, a dose of 0.25 mg/kg, administered over 20-30 seconds and allowing 2 minutes for effect, will usually suffice.

The initial dose of 0.2 mg/kg is recommended for good risk (ASA I) surgical patients over the age of 5 years.

In some patients with severe systemic disease or debilitation, as little as 0.15 mg/kg may suffice.

Narcotic premedication frequently used during clinical trials included fentanyl (1.5-2 ug/kg IV, administered five minutes before induction), morphine (dosage individualized, up to 0.15 mg/kg IM), meperidine (dosage individualized, up to 1 mg/kg IM) and Innovar (0.02 ml/kg IM). Sedative premedications were hydroxyzine pamoate (100 mg orally) and sodium secobarbital (200 mg orally). Except for intravenous fentanyl, administered five minutes before induction, all other premedications should be administered approximately one hour prior to the time anticipated for VERSED induction.

Injectable VERSED can also be used during maintenance of anesthesia, for short surgical procedures, as a component of balanced anesthesia. Effective narcotic premedication is especially recommended in such cases. Long surgical procedures have not been studied.

Incremental injections of approximately 25% of the induction dose should be given in response to signs of lightening of anesthesia and repeated as necessary.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED: All package configurations contain midazolam hydrochloride equivalent to 5 mg midazolam/ml.

- 1 ml ampuls--boxes of 10 (NDC 0004-xxxx-xx);
- 2 ml ampuls--boxes of 10 (NDC 0004-xxxx-xx);
- 1 ml vials--boxes of 10 (NDC 0004-xxxx-xx);
- 2 ml vials--boxes of 10 (NDC 0004-xxxx-xx);
- 5 ml vials--boxes of 1 (NDC 0004-xxxx-xx) and 10 (NDC 0004-xxxx-xx);
- 10 ml vials--boxes of 1 (NDC 0004-xxxx-xx) and 10 (NDC 0004-xxxx-xx);
- 1 ml Tel-E-Ject^(R) disposable syringes--boxes of 10 (NDC 0004-xxxx-xx);
- 2 ml Tel-E-Ject^(R) disposable syringes--boxes of 10 (NDC 0004-xxxx-xx);
- 1 ml Tel-E-Ject^(R) disposable syringe cartridges--boxes of 10 (NDC 0004-xxxx-xx);
- 2 ml Tel-E-Ject^(R) disposable syringe cartridges--boxes of 10 (NDC 0004-xxxx-xx).

THIS PACKAGE INSERT ISSUED (month, year)
 ROCHE LABORATORIES
 Division of Hoffmann-La Roche Inc.
 Nutley, New Jersey 07110

(Code)

Printed in U.S.A.

[End of draft labeling text]

The labeling should be revised exactly as we have requested. Please submit twelve copies of the printed labels and other labeling. If additional information relating to the safety or effectiveness of this drug becomes available before the final printed labeling is submitted to the FDA, further revision of that labeling may be required.

II. BIOPHARMACEUTICS COMMENTS:

1. Protocols 2315, 2152A, 2201A, 2153, 2192, 2135 and 2144 all used unacceptable methods for fitting the midazolam plasma or blood level curves and for determining terminal half-life. There is no indication that an appropriate model was fitted to these data and appropriate criteria established for goodness to fit. The study design and analysis sections simply state that "terminal" points were fitted by "least squares regression". This description is unclear. For example, did the analysis utilize mean linear regression or were polyexponential nonlinear regression fits done? Other analytical issues involve randomness of scatter, weighting of data points, correlation coefficients and other parameters that were never mentioned. The significance of these concerns is that "half-lives" are being reported on data that never reach a log-linear terminus over time and many of the curves appear to be at least triexponential following an intravenous input. The data presented in

summary as Figures 2, 5, 6, 7, and 8 on p.48, 51, 53, and 54 of Volume 1.4 do not seem to fit the conclusion of the investigators that midazolam has a distributive phase that is complete within about one hour and then exhibits a post-distributive log-linear "B" phase. Several of the curves show continuous curvature in semilogarithmic plots. Even the analysis of protocol 943, which did fit a polyexponential to the data, considered data with significant systemic deviation to be "well fit by the biexponential equation."

In a March 29, 1985 conversation with Dr. Crouthamal of Hoffmann-La Roche and Dr. Paul Hepp of this agency, you agreed to address these issues in a timely fashion so that appropriate labeling changes can be made in the future, if necessary.

2. The claim of "linear behavior and dose proportionality" is not established by the data. Since the product is to be titrated and is not for multiple administration, a definitive dose proportionality study will not be required. The labeling should not allow any claims for linear behavior or dose proportionality.

Please submit, in duplicate, the advertising copy which you intend to use in your proposed introductory promotional and/or advertising campaign. Please submit one copy to the Division of Neuropharmacological Drug Products, and the second copy to the Division of Drug Advertising and Labeling, HFN-240, Room 10B-04, 5600 Fishers Lane, Rockville, Maryland 20857. Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission; this form is for routine use, not proposed materials.

In addition, it is required that information and case reports of adverse reactions not previously submitted to your IND or NDA be provided.

Within 10 days after the date of this letter, you are required to amend the application, or notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions concerning this NDA, please contact Mr. Jack Purvis, Consumer Safety Officer, at (301) 443-3830.

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Research and Review
Center for Drugs and Biologics

NDA 18-654

Date Completed: 10 September 1986

CLINICAL CONSULTATIVE REVIEW FROM HFN-160 to HFN-120

Product: Versed (midazolam) Injection
Hoffman La Roche, Nutley, N.J.

Dates: Consult is dated 9 July 1986. Five additional case reports were made available to me by Mr. David Barash of the Division of Drug Experience at an un-recorded later date (see pages 5-7).

Purpose of Consult: Request for Evaluation of Adverse Experience Reports

SUMMARY (Since the new Form FDF 1639's do not have date of submission, the "Date Received by Manufacturer" will be used):

1. "6-4-86", Case 86 02 00589 001. Information for this case report was provided by someone who was not involved in the case and who did not have all of the facts. This is the case of a 30 y. m., weight not stated, who incurred fractures of cervical vertebrae from a car accident. He underwent surgery on the night of the accident and responded well. The surgery is not described, but was probably a cervical spinal fusion.

Two to three days later the patient was scheduled "for repair of a fracture of either the hip or tibia". He was given an induction dose of 20 mg midazolam i.v. (0.28 mg/kg in a 70 kg patient) for an awake intubation. Transtracheal or translaryngeal block, employing topical lidocaine, was also performed, presumably before the administration of midazolam. The intubation is described as unsuccessful. The patient immediately regurgitated, became hypoxic and incurred a cardiac arrest. He was resuscitated but incurred another cardiac arrest later on the intensive care unit and expired.

DISCUSSION: Maintenance of a patent airway during anesthesia in patients with fracture(s) of the cervical vertebrae is very risky because some of the otherwise routine manipulations of the head and neck used to improve the airway can lead to pressure on the cervical spinal cord and possibly quadriplegia. The best way to maintain a patent airway, short of trachostomy, is to catheterize the trachea, a procedure which also offers special risk following cervical spinal injury because this procedure ordinarily involves considerable repositioning of the head and neck. Patients can be intubated awake, but their reaction may also involve a great deal of skeletal muscle movement, which could also injure the spinal cord. Topical anesthetics may reduce the risk from movement during awake intubation, but in turn greatly subdue the protective cough mechanisms which usually act to protect against aspiration. There is simply no good way to manage a case of this type because whatever is done to maintain a patent airway can injure the spinal cord and whatever is done to protect the spinal cord can compromise the airway and/or increase the risk of aspiration. In this case, the greater danger of fatal aspiration from the needed compromises became an unpleasant reality. The risks and choices are too complex to attribute this adverse experience to

SEP 17 1986

use of midazolam, even though the 20 mg dose was more suitable for induction of anesthesia than for "awake intubation".

2. "5-22-86", Case 86 02 00668 001. 73 y. f., estimated weight 40 to 45 kg. This is the case of respiratory arrest and death following a colonoscopy in which midazolam 1 mg was administered twice for sedation. This apparently happened 15 minutes after the last dose of midazolam; the colonoscopy had been completed. The patient also received glucagon and was on an undisclosed amount of haloperidol for chronic maintenance of schizophrenia.

DISCUSSION: The dose of midazolam was relatively low (approximately 0.045 mg/kg total) however, the package insert exerts a maximal effort to warn practitioners not to take even lower i.v. doses of midazolam lightly.

"WARNINGS: PRIOR TO THE INTRAVENOUS ADMINISTRATION OF VERSED IN ANY DOSE, THE IMMEDIATE AVAILABILITY OF OXYGEN AND RESUSCITATIVE EQUIPMENT FOR THE MAINTENANCE OF A PATENT AIRWAY AND SUPPORT OF VENTILATION SHOULD BE ENSURED.....".

In addition, the possible contribution of other drugs to respiratory depression is stressed. It is impossible to make a definitive conclusion from so superficial a narrative, however, it seems most likely that some of the directions for safe use of i.v. midazolam were ignored.

3. "5-16-86", Case 86 02 00648 001. This is a case of trismus developing after administration of 2.5 mg i.v. Versed. Duration: 10 minutes. The patient also received meperidine 50 mg (route not stated). The patient was been prepared for gastroscopy. Administration of Narcan was ineffective (it should not help counteract the effects of midazolam but it might counteract the effects of meperidine).

DISCUSSION: I would not expect trismus from administration of midazolam. The case made for reasonable association in this report is very weak. The patient apparently recovered after being "Treated with Rx Drug". The most reasonable course of action is to be on the lookout for additional adverse experience reports of this type and take no drug regulatory action at this time.

4. "5-2-86", Case 86 02 00587 001. This is the case of a 71 y. f. who received 4 mg of midazolam i.v. to facilitate a colonoscopy; her weight is not available but this seems like neither a very large or very small dose (0.08 mg/kg if she weighed 50 kg). She was on the following medications: Dyazide, Synthroid, aspirin & cimetidine. Meperidine had also been administered i.v. "prior to the adverse experience". She incurred respiratory and cardiac arrest. Resuscitation was successful.

DISCUSSION: The information provided is far from definitive. The term "simultaneous respiratory and cardiac arrest" is made. The credit placed on the word "simultaneous" would depend on the degree of monitoring, something which we know nothing about and are not likely to find out with reasonable effort.

Positions most suitable for colonoscopy, such as the prone jackknife position, are not very suitable for assisted or controlled ventilation of sedated patients. Before undertaking such a procedure in a sedated patient, it is the obligation of the operator to insure that personnel resources for monitoring of ventilation, repositioning the patient in a timely fashion should the need arise and assisting ventilation are adequately provided for. This sort of preparation seems especially indicated in this case because of the patient's age, physical condition, recent administration of i.v. meperidine and the possible weakening effects of chronic medications. I cannot tell from this brief narrative what effort went into preparation for the management of possible complications, but I know of no unusual properties of any of the drugs that would cause cardiac arrest in the absence of neglected ventilation. At any rate, the narrative does suggest recovery.

5. "4-14-86", Case 86 04 00004 001. From This is the case of a 75 y. m., weight not stated, who was admitted to the hospital because of hematemesis. Nothing else about his medical history is revealed. He underwent "laparotomy". Afterwards, on the intensive care unit, midazolam was started by infusion; the reason is not stated but it likely had something to do with facilitating mechanical ventilation. He received 20.8 mg over 3 days. The adverse experience is described as slow recovery of consciousness, signs of "lead pipe" rigidity, hyperreflexia and bilateral leg clonus of 24 hours duration, starting about 2 days after midazolam was discontinued. The patient also received vecuronium at the same time as midazolam, adding support to the conclusion that usage was to facilitate mechanical ventilation.

DISCUSSION: There are insufficient data to evaluate this case, except to note that hematemesis is sometimes associated with bleeding esophageal varices, which in turn is sometimes associated with chronic ethanol abuse; the superficially reported observations could be some variation of ethanol withdrawal or perhaps ethanol and drug(s) withdrawal. I can't say for sure.

6. "4/14/86". Case 85 03 12855 001. From This is the case of a 60 y. m. who received 7 mg i.v. midazolam in preparation for a colonoscopy. Clinical evaluation revealed abnormal blood gases compatible with respiratory insufficiency and a history of chronic bronchitis & emphysema. The patient arrested "immediately after administration" and resuscitation was unsuccessful.

DISCUSSION: The patient's weight is not provided; this dose would represent 0.1 mg/kg in a 70 kg patient. The administered dose could either be large, small or optimum, depending on the patient's response. If the description of the patient's respiratory condition is accurately reported, he was already predisposed to respiratory depression and might

have been less tolerant to midazolam. The U.S. directions for use of i.v. midazolam for conscious sedation have always been quite specific about slow administration to the end point of slurring of speech. In addition, these directions have recently been revised for clarification. It seems probable that these directions were followed in this case. We also do not know what resources were available for immediate management of underventilation or apnea; to judge by the results, they were not adequate.

7. "4/14/86", Case 85 03 12481 001. From

This is the case of a 16 y. m. who received 7.5 mg midazolam and thiopental 15 mg to facilitate rectoscopy. The patient manifested "acute cardiac fibrillation and apnea" 13 hours after midazolam administration. The patient "responded to therapy". Subsequent exposure (presumably to midazolam) was without any problems.

DISCUSSION: The terminology is very confusing; did the patient incur atrial fibrillation or ventricular fibrillation, a big difference?

The time sequence does not make sense. How is this reasonably associated with administration of midazolam 13 hours earlier? It would be a waste of time to say more because there are simply insufficient data to permit evaluation of this case.

8. "4/14/86, Case 86 04 00003 001. From Regional Drug Information Center,

This is the case of a 59 y. m. on the ICU because of atypical pneumonia. He is also described as having nephritis "with a stable degree of renal impairment". The patient apparently received 29 mg midazolam by infusion to facilitate mechanical ventilation (?) over an undisclosed amount of time. Hemiplegia and disorientation was noted after commencing midazolam. The patient is described in one place as recovering on 10/28/85 without treatment and in another place as incurring severe or permanent disability. The duration of this adverse experience is impossible to deduct because the onset date is not available.

Impression: Insufficient data for evaluation. We have not reviewed data to support this "Indication" (unapproved use in the U.S.). If we ever do, this case, as reported, should neither help nor hinder the evaluation.

9. "4-23-86, Case No. 86 02 00564 001. This is the case of a male, described as elderly, age not stated. He received 2 mg midazolam, 50 mg meperidine & morphine (dose not stated) in preparation for a bronchoscopy. The patient expired. No other details are available except that the diagnosis was multiple carcinoma of the lung.

DISCUSSION: The only question that I can pose is why were both morphine and meperidine administered? The possibility of over-premedication comes to my mind. Still, I can make no definitive comments from this preliminary information.

II. Since receiving this consult request, I have been alerted to additional adverse experience reports of this type by Mr. David Wash of the Division of Drug Experience, who knew that I was interested. These will follow:

1. "5/13/86", Case 85 03 12971 001. From the Federal Republic of Germany and it is brief. This is the case of a 75 y. f. who received 10 mg midazolam i.v. for a gastroscopy (weight is not stated but the dose is described as 0.18 mg/kg, which would place her weight at approximately 56 kg). She incurred apnea and cardiac arrest 1 to 2 minutes after receiving the midazolam. Resuscitative efforts were prolonged, requiring endotracheal intubation for 2 hours and a pacemaker for 8 hours. The patient survived with unspecified sequelae after prolonged hospitalization (see check list on form FD 1639).

This patient had a previous thoracoplasty for tuberculosis and may have been more susceptible to complications of underventilation.

DISCUSSION: My only comment on this case is that complications like this should seldom or never occur if practitioners follow the prescription drug labeling approved for use in the United States.

2. "5/28/86", Case 85 04 00025. From the United Kingdom. This is the case of a 61 y. m. with hematemesis secondary to esophageal varices. He had coagulopathies secondary to hypovitaminosis K. The esophageal varices were judged to be secondary to ethanol abuse of long standing.

He received 5 mg of midazolam for induction of general anesthesia. Planned surgery is not stated; my guess is that it was for surgical treatment of esophageal varices. The sequence afterwards was as follows: He became restless, agitated, required restraints, sneezed, clenched his jaw, rolled his eyes, manifested first shallow & spasmodic breathing and then progressive cyanosis. He was given succinylcholine and then both succinylcholine and atropine. Relaxation was never adequate but he was intubated anyway. He arrested and was resuscitated for 30 minutes. Resuscitation was unsuccessful.

DISCUSSION: This could represent a severe adverse experience of the type sometimes referred to as "central anticholinergic syndrome". Some adverse experiences of this type have been presumed possibly or probably associated with administration of benzodiazepines, although these drugs are not usually considered anticholinergics.

One of the most problematic drugs for "central anticholinergic syndrome" is atropine. If this case represents a severe form of this syndrome, the later administration of atropine may have unfavorably altered the outcome. If it had been absolutely necessary to administer an anticholinergic, glycopyrrolate would have been a much

better choice since the "blood-brain barrier" is relatively resistant to crossing of glycopyrrolate.

Other less likely mechanisms might include delirium tremens or undiagnosed malignant hyperthermia. The latter comes to mind mainly because of the failure of succinylcholine to produce adequate skeletal muscle relaxation for endotracheal intubation.

All of this is pure speculation. The most likely speculation is that we will never know for sure!

3. "5/13/86", Case 85 03 12970 001. From Federal Republic of Germany. This is the case of a 69 y. m. who received 5 mg midazolam i.v. (0.08 mg/kg) as premedication for "catheterization" (catheterization of what, bladder, heart??). He was on haloperidol, dose not stated, chronically ("t.i.d.") and also received "3 X 2 caps" of chlormethiazole. Past history revealed chronic ethanol abuse, suspected encephalopathy and nicotine abuse. The patient was judged severely restless prior to the administration of midazolam. He incurred apnea and cardiac arrest 3 to 4 minutes after receiving the midazolam. The patient was resuscitated but he manifested apnea again six hours later, "leading to death".

DISCUSSION: This case brings about questions of clinical judgement which it are impossible to answer from the available information. It seems most likely that respiratory arrest preceded cardiac arrest. The use of another depressant drug (haloperidol) may have enhanced the chances of underventilation, as could ethanol abuse and the secondary effects of chronic smoking. AS practitioners are warned by the U.S. package insert, those who administer midazolam i.v. in any dose should be prepared to manage underventilation.

4. "5/13/86", Case 85 03 12784 001. From Federal Republic of Germany. This is the case of an 81 y. m. who received 7.5 mg midazolam slowly i.v. (0.12 mg/kg) for postoperative sedation, 5 days following a laparotomy. Respiratory depression occurred 10 minutes later. The patient was intubated and received artificial respiration for 10 hours. Death occurred two days later with symptoms of toxic circulatory failure. The relationship, if any, of the administration of midazolam and the fatal outcome is unclear from the available information.

Impression: Insufficient data for evaluation. Midazolam is not approved for postoperative sedation in the U.S. Why sedate a patient at a time when he or she is supposed to be recovering from the effects of previously administered central nervous system depressants? If there is an unusual reason for sedation in this case, why use a dose large enough to facilitate endoscopy?

5. "5/13/86. Case 85 03 12365 001. From Federal Republic of Germany. The patient is described as being greater than 80 years of age, sex unknown. Midazolam 4 mg was administered i.v. as premedication for gastroscopy. The rest of the narrative is even more superficial: "Patient experienced respiratory arrest and expired after administration of Versed."

Impression: Insufficient data for evaluation.

In addition to these cases, I was informed by Dr. Del Vecchio of ROCHE (telephone conversation of 9 June 1986) that there are 6 deaths involving European clinical investigation of midazolam as part of the treatment of status epilepticus. He was preparing to submit them to the FDA. I have not seen these reports, however, I could contribute very little unless they contain more information than the other European reports.

CONCLUSIONS:

1. I have gone over these cases three times, once with Drs. Katz & Collins of HFN-120 and twice in the preparation of this summary. From these evaluations, I have concluded that intravenous midazolam is safe and effective if used as labeled in the United States. It is not surprising to see cases of underventilation or apnea following intravenous administration of a drug which is suitable in larger doses for induction of general anesthesia. All of this was taken into consideration in preparation of the original prescription drug labeling. The WARNINGS section starts off with a statement that clinicians should be prepared to manage underventilation prior to the administration of any dose of i.v. midazolam. Disease states which might make patients more sensitive to the effects of i.v. midazolam are discussed. The fact that induction doses decrease with age is noted.

2. I therefore conclude that some practitioners who use midazolam to facilitate endoscopy are not competent by training and/or preparation to administer intravenous drugs which may depress respiration. The primary problem in these cases appears to be ventilatory, with hypoxic circulatory effects appearing only secondary to respiratory depression. ROCHE has been aware of this problem; this has led them to revise the prescription drug labeling in accordance with 21 CFR 314.70 (c) (2) (iii). The revision was by way of a supplement dated 20 June 1986. The DOSAGE AND ADMINISTRATION directions for conscious sedation were revised for clarification, with the intent of placing the revision in all stock samples on or after 15 July 1986. The new directions clarify how the drug is to be titrated slowly to the effect of slurring of speech, stresses the

use of fractional small doses of approximately 0.035 mg/kg, defines slow administration as to time and clarifies that 0.1 to 0.15 mg/kg is a usually adequate total dose.

The effect of this revision on the incidence of future adverse experiences remains to be determined. This will depend not only on the revision but also on the educational program which ROCHE uses as a followup to the revision.

3. Cases of other types also appear. Each case is accompanied by a Discussion, which need not be repeated here. Some adverse experiences have to do with uses which have not been reviewed by the U.S. FDA, mainly longer term use to facilitate mechanical ventilation. No drug regulatory action, based upon these cases, is indicated at this time, but these cases may need to be considered in the event of a future application for this usage.

4. The following other cases are unusual:

a. Case I-3, page 2 of this review, is an adverse experience superficially reported as trismus. The narrative falls far short of establishing reasonable association with administration of midazolam but we might ask ROCHE to be on the lookout for similar cases.

b. Case II-2, page 5 of this review describes a severely ill patient with probable complications of ethanol abuse. This case might represent a severe "central anticholinergic syndrome" (see DISCUSSION), delirium tremens, drug(s) withdrawal and/or malignant hyperthermia following succinylcholine administration. This case may be of later interest to us if future cases establish that midazolam can be associated with "central anticholinergic syndrome".

4. The recommendations for reducing dosage in elderly patients was based upon studies of patients with disease states, the fact that induction doses decrease with age and the fact that the efficiency of organ system function decreases with age. This should be sufficient directions for the prudent practitioner, however, the sponsor might be asked if more specific dosage experience in the elderly has accumulated since the original submission of the new drug application.

RECOMMENDATIONS:

In form of a potential letter to the sponsor:

1. We ask that you schedule a meeting with us to discuss the efficacy of your 20 June 1986 supplement, and any educational program which might have accompanied that 21 CFR 314.70 (c) (2) (iii) prescription drug labeling revision, in reducing the incidence of poorly managed

underventilation or apnea following administration of i.v. midazolam for conscious sedation. The need, if any, to take additional steps can be discussed at that meeting.

2. There has been speculation (Medical Letter, Vol. 28, Issue 719, August 1, 1986) that current dosage recommendations for midazolam may be too high for some patients, especially the elderly. Please evaluate data on use in elderly patients, which may have accumulated since the original submission of the NDA, for cases of unusual dosage response.

3. Case 86 02 00648 001, dated "5-16-86", is a case of trismus developing after administration of 2.5 mg i.v. midazolam. Though this case, as reported, does not establish a reasonable association, we ask that you be on the alert for similar cases.

4. Case 85 04 00025 describes restlessness, agitation, counterproductive skeletal muscle movements, etc. following administration of midazolam for induction of general anesthesia. In addition, atypical response to succinylcholine is noted. The etiology of this severe adverse experience is unclear, but it may represent ethanol &/or drug(s) withdrawal, malignant hyperthermia and/or a severe form of "central anticholinergic syndrome". The latter has been reported for other benzodiazepines, although these drugs are not usually considered anticholinergics. Please be on the alert for cases which may represent "central anticholinergic syndrome".

We also note that atropine was administered after the onset of this adverse experience, a drug which can precipitate "central anticholinergic syndrome".

5. We note three non-U.S. complications which occurred or may have occurred following subacute administration of i.v. midazolam to facilitate mechanical ventilation on the intensive care unit (Cases 86 00004 001, dated "4-14-86", 86 04 00003 001 and 85 03 12784 001, dated "5/13/86"). This use has not been reviewed by this agency and there is no other reason why these cases should currently be of drug regulatory interest. However, an application for usage of this type is possible in the future. If feasible, additional followup on these, and any similar cases which may accumulate, is recommended for inclusion in any such future application.

David Lawrence Scally
David Lawrence Scally, M.D.
Medical Officer, HFN-160

NDA 18-654

HFN-160 Consult File

HFN-120

R/D DLScally 9/10/86

R/D Init. by CRodriguez/JCKanealy 9/10/86, RWalters/PHRussell 9/10/86

Doc. Room 160

Challicky
for Dr. J. E. Kanealy
9/10/86
PHR
9-10-86

NDA 18-654/S-012AM

Date Completed: 27 October 1987

CLINICAL REVIEW & EVALUATION OF LABELING
and
POTENTIAL "DEAR DOCTOR" LETTER

Sponsor: Roche of Nutley, N.J.

Name of Product: VERSED (midazolam HCl) Injection

Date of Submission: 23 October 1987

Received by HFN-160: 26 October 1987

Related Documents: See my previous review of S-012, dated 7 October 1987, for background information. See also the resulting letter to the sponsor, dated 9 October 1987.

CLINICAL SUMMARY:

The sponsor has considered our letter dated 9 October 1987. In that regard, they will add a boxed WARNING to the package insert, a request which they had previously opposed. They will also issue another "Dear Doctor" letter, something which they have expressed an interest in all along. Some of the text suggested in the 9 October 1987 letter has been revised and they have explained their reasons quite clearly. The covering letter also provides the outline for an educational program which should enhance safe usage of intravenous midazolam.

I have carefully evaluated this latest version of a potential revised package insert. It is my belief that this version contains all of the known information needed for safe administration of intravenous midazolam. While I wish to reserve the right to bring up points for discussion at any meetings with FDA Staff, or at any meetings between FDA Staff and Roche, none of the discussion which I have in mind is worth causing any delay in the dissemination of a revised package insert, new "Dear Doctor" letter, etc. For this reason, I am making only two recommendations for minor editorial change, recommendations which can hardly be considered controversial:

ADVERSE REACTIONS:

a. Change: "The following adverse reactions were reported after intramuscular administration:"

To: "The following additional adverse reactions were reported after intramuscular administration:"

b. Change: "The following adverse reactions were reported subsequent to intravenous administration:"

To: "The following additional adverse reactions were reported subsequent to intravenous administration:"

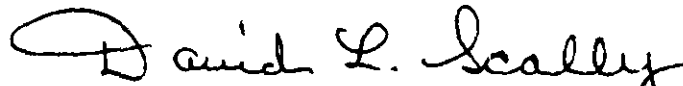
In the unlikely event that these recommendations are controversial, and might cause delays, they should be dropped.

CONCLUSION & RECOMMENDATION:

An approvable letter concerning the draft package insert and "Dear Doctor" letter contained in this supplement should issue. That letter should include the two minor editorial recommendations cited in my review, though this can be deleted if it will cause delay in finalization of the supplement.

The final printed package insert should be disseminated under 21 CFR 314.70 (c), a provision concerned with "Supplements for changes that may be made before FDA approval."

In addition, the submitted final printed labeling should include information as to the mailing lists selected for dissemination of the "Dear Doctor" letter. Previous conversations with the sponsor suggest that the audience will be wider than for the first "Dear Doctor" letter, however, a record of the final lists selected should be preserved.



David Lawrence Scally, M.D.
Medical Officer, HFN-160

0616z
dls/DLS
27 October 1987

NDA 18-654/S-012AM
HFN-160
Doc Rm 160
HFN-340
R/LDLSally 10-27-87
R/D init by JCKenealy 10-28-87; PGWalters 11-5-87
FT/MPD/11-9-87

11/25/87
RW 11/5/87



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857
June 11, 1986

Loretta M. Itri, M.D., F.A.C.P.
Director
Clinical Safety Surveillance Dept.
and Clinical Oncology Program
Hoffmann-La Roche Inc.
Nutley, NJ 07110

Dear Dr. Itri:

In response to your letter of June 3 regarding foreign reports of adverse events associated with the use of Yersed^(R) I am acknowledging receipt of these reports.

The six reports of death only, with no reaction given, which occurred in a foreign clinical trial, are not reportable to FDA under 21 CFR 314.80. However, we expect you would analyze them for an increased frequency of deaths, from whatever cause, when the periodic reporting cycle ends. The FDA 1639 forms should not be submitted to FDA.

The remaining reports all describe serious events. If these reports describe events not in the current package circular, they should be submitted as 15-Day reports under 21 CFR 314.80. I am returning them for your analysis. If they in fact meet the criteria for 15-Day reports, they should be sent in duplicate to:

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

within 15 days of the time when such a determination is made. If the events described are in the package circular, no FDA-1639 forms should be submitted. However, these events should be analyzed for an increase in frequency at the close of the periodic reporting cycle.

Thank you for your efforts to comply with the regulations.

Sincerely yours,

Julie B. Milstien, Ph.D.
Acting Chief, Reports Evaluation Branch
Division of Epidemiology and
Surveillance (HFN-730)
Office of Epidemiology and Biostatistics
Center for Drugs and Biologics
(301) 443-4580

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JUN 13 1986

Clinical Safety Surveillance

Enclosures