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APPLICATION NUMBER:NDA 20-942

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-942	CODE: 1P
NAME: Versed® (Midazolam Hydrochloride) Oral Syrup 2mg/mL	
SPONSOR: Hoffmann-La Roche Inc., 340 Kingsland Street, Nutley, New Jersey 07110	
SUBMISSION TYPE: Original NDA	SUBMISSION DATE: February 4, 1998
REVIEWER: Suresh Doddapaneni, Ph.D.	

SYNOPSIS

Versed® (Midazolam HCL) has been in use since 1986 in the United States (NDA 18-654) in adults for conscious sedation/anxiolysis/amnesia following IV and IM administration. It is also indicated following IV administration, for the induction of general anesthesia and as a continuous infusion in intubated, mechanically ventilated patients, during anesthesia and/or in a critical care setting. Outside the U.S., a midazolam 15 mg oral tablet formulation (Dormicum®) has been approved for use as a hypnotic. Although not indicated, midazolam has been used in pediatrics as a premedicant by mixing the midazolam injectable solution with flavored syrups or juices, to mask the bitter taste, for subsequent oral administration to pediatric patients. A supplement addressing the sedation of pediatric patients following IV and IM midazolam administration was approved on March 18, 1997. Roche developed the Versed® oral syrup, subject of the current NDA, to address FDA's request that an oral dosage form for midazolam in pediatric patients be developed. Versed® syrup is indicated for sedation, anxiolysis and amnesia prior to diagnostic, therapeutic or endoscopic procedures or before induction of anesthesia. The recommended dose is 0.5 mg/kg (not to exceed 20 mg) with up to 1.0 mg/kg in younger patients (6 months to <6 years of age) and as low as 0.25 mg/kg in older patients (6 to <16 years of age).

The data submitted in this NDA consists of two studies (one each of clinical and pharmacokinetic studies) conducted in pediatric population using the to-be-marketed Versed® oral syrup, data acquired by the sponsor earlier in support of NDA 18-654, and literature articles. Data summarized from published studies in adults indicates that midazolam undergoes oxidative metabolism mediated by cytochrome P450III A4 isozyme to a major and active metabolite, α -hydroxymidazolam. Binding of midazolam and α -hydroxymidazolam to albumin is about 96.5% and 89.4% respectively. A number of published studies, conducted in adult subjects, using effect compartment PK/PD modeling (sigmoidal E_{max} model), consistently demonstrated a strong correlation between plasma midazolam concentrations and surrogate CNS effects (EEG, digit symbol substitution test, reaction time, tracing errors, saccadic eye movement, visual evoked response, drowsiness etc.) in doses ranging from 0.03 mg/kg to 0.15 mg/kg IV and 15 mg oral midazolam. Published reports also show that α -hydroxymidazolam is equipotent to midazolam and contributes significantly to the efficacy of midazolam after an oral dose compared to an IV dose (AUC_{0-∞} ratio of α -hydroxymidazolam to midazolam after an oral dose is about two fold higher than after an IV dose).

In a study conducted by the sponsor (protocol 15323) in pediatrics stratified into three groups of 6 months to <2 years, 2 years to <12 years, and 12 years to < 16 years, the general pharmacokinetics and dose-proportionality of three oral doses of 0.25, 0.5, and 1.0 mg/kg

Versed® syrup, absolute bioavailability of a 0.50 mg/kg dose of Versed® syrup, and general IV pharmacokinetics of a 0.15 mg/kg midazolam dose were determined. The absolute bioavailability of 0.50 mg/kg oral dose was about 35%. Dose-linearity was demonstrated in the dose range of 0.25 to 1.0 mg/kg across the age range of 6 months to 16 years. Dose-linearity was also demonstrated within the age group of 2 years to <12 years across the three age groups. The $AUC_{0-\infty}$ ratio of α -hydroxymidazolam to midazolam for the oral dose in pediatric patients was higher than for an IV dose (0.38 to 0.75 versus 0.21 to 0.39 across the age group of 6 months to <16 years). IV data indicated that pediatrics in general have a higher clearance than adults. No change in pediatric pharmacokinetics with age was apparent, although this could be due to not having sufficient patients in the age groups of 6 months to <2 years and 12 years to <16 years. Pharmacokinetic data suggests that the optimum dose is likely to be 0.25 mg/kg and not 0.5 mg/kg as the sponsor is recommending. Pharmacokinetic data also suggests that the sponsor's recommendation of a higher dose of 1.0 mg/kg in pediatric patients 6 months to <6 years may not be appropriate and the same dose of 0.25 mg/kg can be used in this sub group as well.

Published studies on drug-drug interactions in adults indicate that CYP3A4 inducers such as rifampin and carbamazepine decreased the C_{max} and AUC of orally administered midazolam by about 95% while CYP3A4 inhibitors such as erythromycin, diltiazem, verapamil, ranitidine, cimetidine, itraconazole, fluconazole, and ketoconazole markedly increased the C_{max} and AUC of orally administered midazolam. The increases in C_{max} and AUC, respectively, of midazolam were, 170% and 341% with erythromycin, 105% and 275% with diltiazem, 97% and 192% with verapamil, 240% and 980% with itraconazole, 150% and 250% with fluconazole, and 309% and 1490% with ketoconazole. Pretreatment with grapefruit juice was reported to result in a 56% and 52% increase in C_{max} and AUC, respectively, of oral midazolam. Published studies in hepatic failure patients indicate that chronic hepatic disease alters the pharmacokinetics of midazolam. Following IV administration, the clearance of midazolam was reported to be reduced by about 40-50%, and the elimination half-life was increased by about 90-100% in patients with alcoholic cirrhosis compared with subjects having normal hepatic function. After oral administration, C_{max} and bioavailability were reported to be increased by about 43% and 100% respectively. Although the pharmacokinetics of intravenous midazolam in patients with chronic renal failure differed from those of subjects with normal renal function, there were no alterations in the distribution, elimination, or clearance of unbound drug in the renal failure patients. However, the accumulation potential of the major and active metabolite α -hydroxymidazolam which is excreted in the urine as a glucuronide is unknown.

Recommendation

Section 6.0 of NDA 20-942 submitted on February 4, 1998 meets the Agency's Clinical Pharmacology and Biopharmaceutics requirements. Therefore, from the viewpoint of the Office of Clinical Pharmacology and Biopharmaceutics, NDA 20-942 can be approved provided a mutually agreeable package insert (pharmacokinetics section) between the Agency and the sponsor can be worked out.

/S/ 6/18/98

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1. BACKGROUND

Versed® (Midazolam HCL) has been in use since 1986 in the United States (NDA 18-654) for conscious sedation/anxiolysis/amnesia prior to diagnostic, therapeutic, and endoscopic procedures following IV and IM administration. It is also approved for the induction of general anesthesia following IV administration and as a continuous IV infusion in intubated, mechanically ventilated patients, during anesthesia and/or in a critical care setting. Outside the U.S., a midazolam 15 mg oral tablet formulation (Dormicum®) has been approved for use as a hypnotic.

Currently, there is no commercially available midazolam oral dosage form approved in the United States. Although not indicated, there is an extensive off-label use of midazolam in pediatric patients by mixing the midazolam injectable solution with flavored syrups or juices, to mask the bitter taste, for subsequent oral administration to pediatric patients. Compounding of oral midazolam solutions from the parenteral formulation is potentially problematic because of the pH-dependent water solubility of midazolam and the potential use of grapefruit juice as a vehicle. At the March 1, 1994 Anesthetic and Life Support Advisory Committee meeting, a request was made to the sponsor that available IV and IM data in pediatric patients be submitted and that an oral dosage form be developed. In response to the above, a supplement addressing the sedation of pediatric patients following IV and IM midazolam administration was submitted to the Agency on September 28, 1995 and subsequently approved on March 18, 1997. Roche developed the Versed® oral syrup, subject of the current NDA, to address the FDA's request that an oral dosage form for midazolam be developed. Currently, Versed® syrup is not approved in any other country and no applications have been withdrawn or are pending outside the U.S.

2. OVERVIEW OF THE NDA

The primary objectives of the clinical plan for this pediatric oral syrup dosage form were to obtain additional information to improve dosing guidelines and to further characterize the safety and efficacy profile of oral midazolam in the target pediatric population. The basis for these objectives is that the safety and efficacy of IV and IM midazolam as premedicant in pediatric patients was already demonstrated earlier by the sponsor in the supplement that was approved on March 18, 1997.

The data submitted in this NDA consists of two studies (one each of clinical and pharmacokinetic studies) conducted in pediatric population using the to-be-marketed Versed® oral syrup, data acquired by the sponsor earlier in support of NDA 18-654, and literature articles. The clinical trial (protocol NR15345) evaluated the safety and efficacy of the Versed® oral syrup in about three hundred and ninety seven (397) pediatric patients. The pharmacokinetic study (protocol NR15323) conducted in about one hundred and eleven (111) pediatric patients characterized the absolute bioavailability, general pharmacokinetics, and dose-proportionality aspects of the oral syrup. In addition, sponsor summarized results from about one hundred and

one (101) published articles and nine technical reports from Hoffman La Roche. Information on the metabolism, protein binding, drug-drug interactions, special populations (renal failure, hepatic failure etc.) was summarized from studies conducted in adults (i.e., other than the aspects covered in protocol NR 15323, no other studies were specifically conducted in pediatrics).

2.1 RATIONALE FOR USE OF ORAL MIDAZOLAM AS A PEDIATRIC PREMEDICANT

The aim of premedication is to establish or maintain mental and emotional relaxation, reduce sensory input and metabolic rate and suppress adverse reactions of the autonomic nervous system. Premedication allows the patient to enter the procedure room with minimal apprehension, sedated but easily aroused and cooperative without untoward side effects. Overall, premedication results in a less traumatic medical experience for the patient. The need for a premedicant is often greater in children than in older patients due to heightened fears of bodily harm, communication limitations, and difficulties distinguishing between reality and fantasy. Separation from parents also brings about a strong feeling of anxiety. Since IV and IM routes are painful and increase the level of anxiety in children, oral route is preferred by children (more convenient as well). In contrast to other benzodiazepines, midazolam can be prepared as a water-soluble formulation for both parenteral and oral use.

2.2 RATIONALE FOR DOSE OF MIDAZOLAM

Based on established efficacious IM doses (0.10 to 0.15 mg/kg) for pediatric patients and an estimated 21% bioavailability of oral midazolam, oral doses of 0.48 to 0.71 mg/kg would be predicted to yield a midazolam concentration-time profile similar to 0.10 to 0.15 mg/kg IM midazolam. Therefore, doses of 0.25, 0.50, and 1.0 mg/kg were tested in the two studies submitted in this NDA to produce sub-optimal, optimal, and slightly excessive pharmacologic effects. This strategy was used to develop dosing guidelines and to characterize the safety and pharmacokinetic profile of midazolam.

2.3 FORMULATION

The two pivotal studies were conducted using the to-be-marketed formulation. It contains 2.0 mg of midazolam per mL at a pH of 3.2 ± 0.3 . The composition of the formulation is shown in table 1 with an explanation of the function of each of the ingredients.

Table 1. Composition of Versed® oral syrup.

Ingredients	Function	Syrup content (gm/100mL)
✓ Midazolam	Active	
✓ Hydrochloric acid	Solubilizer	
✓ Sorbitol solution 70% (w/w)	Sweetener	
✓ Glycerin	Thickener, sweetener, Anticaking agent	
✓ Citric acid anhydrous	Buffer system component	
✓ Sodium citrate	Buffer system component	
✓ Sodium Benzoate	Preservative	
✓ Sodium saccharin	Sweetener	
✓ Disodium edetate	Chelating Agent	
✓ D&C Red #33	Colorant	
✓ Artificial cough syrup flavor #134681	Flavoring agent	
✓ Artificial bitterness modifier # 36734	Bitterness modifier	
Purified water	Vehicle	mL

3. METABOLISM

Metabolism and excretion information summarized below pertains to studies conducted in adults and not specifically conducted in pediatric patients. Midazolam is primarily metabolized by oxidation at the 1- or alpha- position mediated by cytochrome P450III A4 in the liver and gut, followed by glucuronidation of the α -hydroxyl metabolite. α -Hydroxymidazolam is present in both unconjugated and conjugated forms in human plasma (1, 22, 28). It is excreted in urine as the glucuronide to the extent of 63% to 80% of the total midazolam dose (12, 24, 26, 27). Midazolam is also metabolized to two other minor metabolites. The 4-hydroxy metabolite (about 3% of the dose) and 1,4-dihydroxy metabolite (about 1% of the dose) are excreted in small amounts in the urine as conjugates (22).

The extent of binding of midazolam to albumin is moderately high and concentration independent (upto 10 μ g/mL). The free fraction of midazolam in plasma varies between 2.3 and 6%, but generally is between 3.5% to 3.7% (2, 41, 42, 43, 44). The midazolam blood to plasma ratio is 0.53 (24).

In one study in which the free fraction of both α -hydroxymidazolam and midazolam in plasma were determined in healthy volunteers, the free fraction of α -hydroxymidazolam was higher (10.6 \pm 0.6%) than that (2.4 \pm 0.12%) of midazolam (43).

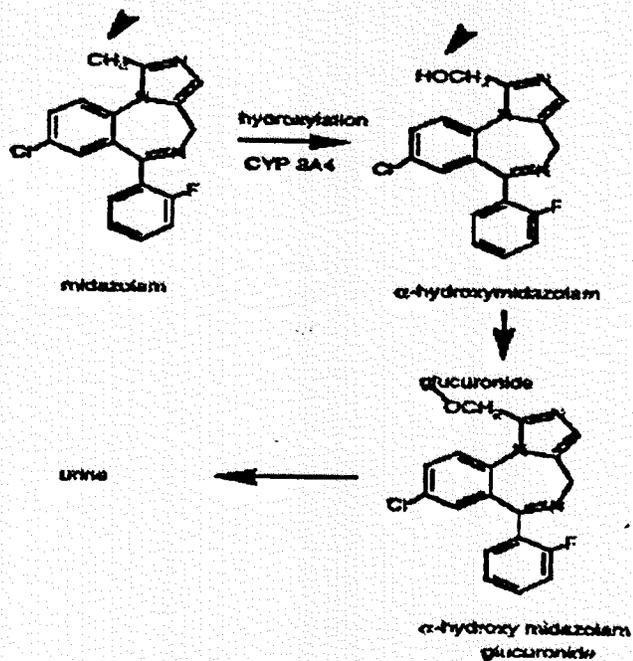


Figure 1. Schematic of the partial metabolic pathway of midazolam.

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4. ANALYTICAL METHODOLOGY

5. PHARMACOKINETIC AND PHARMACODYNAMIC EVIDENCE FOR THE EFFICACY OF ORAL MIDAZOLAM

Midazolam and α -hydroxymidazolam exert the pharmacologic effects via a reversible interaction with GABA benzodiazepine receptor in the CNS. A number of published studies, conducted with adult subjects, using effect compartment PK/PD modeling (sigmoidal E_{max} model), consistently demonstrated a strong correlation between plasma midazolam concentrations and surrogate CNS effects (EEG, digit symbol substitution test, reaction time, tracing errors, saccadic eye movement, visual evoked response, drowsiness etc.) in doses ranging from mg/kg to mg/kg IV. A summary of these results is presented in Table 2. As can be expected, the EC_{50} values vary with different effect measures. After IV administration, there is a short equilibrium delay between the achievement of threshold concentrations and the effect. The half-time of equilibration exit rate constant of the effect compartment (K_{∞}) was 1 to 5 minutes. Although the clinical end point for this product is degree of sedation, it has to be noted that these studies were conducted in healthy volunteers and therefore difficult to relate to the clinically relevant drug effects (sedation, anxiolysis, cooperation, time to recovery etc.) However, collectively these studies do provide evidence of the efficacy of midazolam. Although, *in vitro* studies reported that α -hydroxymidazolam is half as potent as midazolam, an *in vivo* study where α -hydroxymidazolam was administered intravenously demonstrated that E_{max} and EC_{50} of midazolam and α -hydroxymidazolam are equivalent (43). A full copy of this article (reference 43) is attached in appendix III at the end of the list of references. Although, oral midazolam produces

is attached in appendix III at the end of the list of references. Although, oral midazolam produces the same pharmacologic effects as IV or IM midazolam, the dose needed, and the onset and duration of action will be influenced by differences in bioavailability, relatively higher concentrations of α -hydroxymidazolam, and the kinetics of oral drug absorption and disposition. In contrast to rapid IV administration of midazolam, with oral administration of midazolam, the rate of midazolam absorption is slow compared to effect compartment equilibration. Consequently, an equilibrium delay is not observable. Two studies of oral midazolam did not consider the contribution of α -hydroxymidazolam to the pharmacologic activity of oral midazolam thus noting a longer equilibration delay (64, 91). Formation of α -hydroxymidazolam most likely delayed the peak effect of oral midazolam, resulting in a longer equilibration delay. However, when α -hydroxymidazolam was taken into account, no delay between concentration and effect was observed with oral midazolam (12).

Table 2. Summary of results of PK/PD modeling studies with IV and PO midazolam and IV α -hydroxymidazolam.

# subjects/Dose	Effect Measures	EC ₅₀	Hill Exponent	T _{1/2, eff} (min)	Reference
Midazolam -IV 8/3x0.05 mg/kg	Cardiovascular Respiration	51 53	-		92
10/0.1 mg/kg	EEG (% β)	40 \pm 2.8	2.5 \pm 0.4		93
8/15 mg over 5 minutes	EEG (β)	290 \pm 98	3.1 \pm 1.0		94
3/7.5, 15, and 25 mg at 5 mg/min	EEG	152 \pm 48	1.9 \pm 0.2		95
12/0.03 or 0.07 mg/kg	Digit symbol substitution test	16-21	-		96
20 patients/ 0.42mg every 10 minutes, then 0.125 mg/kg/h	Name/birth date Space/time Drowsiness Partial amnesia	173 168 116 81	-		97
6/0.15 mg/kg	Reaction time Tracing errors	104 171	1.25 1.27		12
8/0.1 mg/kg	EEG (β) Saccadic eye movement	77 \pm 15 40 \pm 7	3.1 \pm 0.3 4.5 \pm 1.2		43
<u>α-Hydroxy Midazolam-IV</u>					
8/0.15 mg/kg	EEG (β) Saccadic eye movement	98 \pm 17 49 \pm 10	3.1 \pm 0.5 4.7 \pm 1.0		43
Midazolam-oral 6/15 mg	EEG (α) Visual evoked response P-100	42 \pm 36 48 \pm 34	3.7 \pm 1.8 2.9 \pm 1.4		91
6/15 mg on 4 occasions	EEG (% α) Visual evoked response P-100	40-67 25-51	1.7-1.7 2.8-3.2		64

5.1 ROUTE DEPENDENT CONTRIBUTION OF α -HYDROXYMIDAZOLAM TO THE THERAPEUTIC EFFECTS OF MIDAZOLAM

Following IV or IM administration, the plasma concentrations of α -hydroxymidazolam are low compared to those of midazolam. The ratio of the AUC of α -hydroxymidazolam to the AUC of midazolam ranges from Because of these low levels, its contribution to the pharmacologic effects of IV midazolam may not be substantial. In contrast, because of the extensive first-pass metabolism, α -hydroxymidazolam concentrations are substantially higher (about 50% of those of midazolam) after oral administration. The ratio of the AUC of α -hydroxymidazolam to the AUC of midazolam ranges from therefore, it is expected to contribute substantially to the pharmacologic effects of oral midazolam. Based on the EC_{50} and relative plasma concentration of α -hydroxymidazolam, contribution of α -hydroxymidazolam to the observed pharmacodynamic effects is estimated to be about 10% after IV administration and about 34% after oral administration of midazolam in adults. In a published article, no statistically significant differences were detected between the pharmacodynamic parameters (EC_{50} and E_{max}) of midazolam and α -hydroxymidazolam, indicating that α -hydroxymidazolam is equipotent and equally effective as unchanged midazolam on a total plasma concentration basis.

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6. PHARMACOKINETICS OF MIDAZOLAM IN PEDIATRIC PATIENTS

Although oral midazolam produces the same pharmacologic effects as IV and IM midazolam in pediatric and adult patients, the required dose, onset, intensity and duration of drug action may be influenced by differences in bioavailability, concentrations of α -hydroxymidazolam,

drug absorption, dose-dependent pharmacokinetics in pediatric patients, and changes in pharmacokinetics with increasing pediatric age.

Therefore, the objectives of pharmacokinetic study NR15323 were to characterize the pharmacokinetics, dose-proportionality, absolute bioavailability of oral midazolam. To this effect, study was conducted as a three arm study-Arm I evaluated the dose-proportionality aspects of the oral syrup in age stratified pediatric patients (0.25, 0.5, 1.0 mg/kg doses)-sedation and anxiolytic scores were also obtained in this arm; Arm II evaluated the absolute bioavailability of the oral syrup with oral (0.5 mg/kg) and IV (0.15 mg/kg) doses given to age-stratified pediatric patients in a cross-over fashion; Arm III evaluated the IV pharmacokinetics of midazolam (0.15 mg/kg dose).

6.1 PHARMACOKINETICS AND DOSE-PROPORTIONALITY OF ORAL DOSES OF VERSED SYRUP (ARM I)

The objective of this arm was to characterize the oral pharmacokinetics of midazolam and α -hydroxymidazolam and to determine the dose-proportionality. This was a multicenter, observer blind, parallel group study, in which eighty five (85) pediatric patients (in-patients and out-patients, requiring a sedative for day-stay or minor procedures) were randomized to receive one of the three single oral doses of midazolam. The pediatric patients were stratified by age (6 months to <2 years, 2 to <12 years and 12 to <16 years and were randomly assigned to receive either 0.25 mg/kg, 0.50 mg/kg, or 1.0 mg/kg of midazolam (total oral dose not to exceed 40 mg). Midazolam was administered at least 30 minutes before the procedure. Blood samples were collected for 10 hours following administration of midazolam. Sedation of the patient was recorded using a five-point sedation scale (1=alert/active; 2=awake/calm; 3=drowsy; 4=asleep (does not respond to name/commands but responds to mild shaking); 5=asleep (does not respond to name/commands or mild shaking) until satisfactory sedation was achieved or up to 30 minutes. Anxiolysis was assessed using a four-point anxiolysis scale (1=poor; 2=fair; 3=good; 4=excellent) at the time of separation from parents or at the time of mask induction for patients undergoing general anesthesia. **No mathematical modeling of the relationship between plasma concentrations and sedation or anxiolytic effects was attempted.**

Figure 2 displays the mean plasma concentration versus time profile of midazolam and α -hydroxymidazolam following oral administration of 0.25, 0.50, and 1.0 mg/kg of midazolam syrup in pediatric patients. Tables 3 and 4 list the pharmacokinetic parameter values for midazolam and α -hydroxy midazolam after the administration of single oral doses of 0.25, 0.5, and 1.0 mg/kg in the same patients. In the age group 6 months to <2 years only one patient each received the dose in the respective three dose groups (note: clinical study has 147 patients in this age group). Therefore, in this section statistical analysis involving this group should be interpreted with caution.

Midazolam was readily absorbed in pediatric patients after oral administration of midazolam syrup. Mean t_{max} values ranged from 0.17 to 0.35, 0.72 to 0.95, and 0.55 to 2.65 hours for age groups 1, 2, and 3, respectively. In adults receiving 0.10 to 0.57 mg/kg midazolam solution or tablet, the mean t_{max} values ranged from 0.37 to 1.6 hours (23, 24, 51, 52, 53, 54, 59, 60, 61, 62, 64, 65, 66, 67, 68).

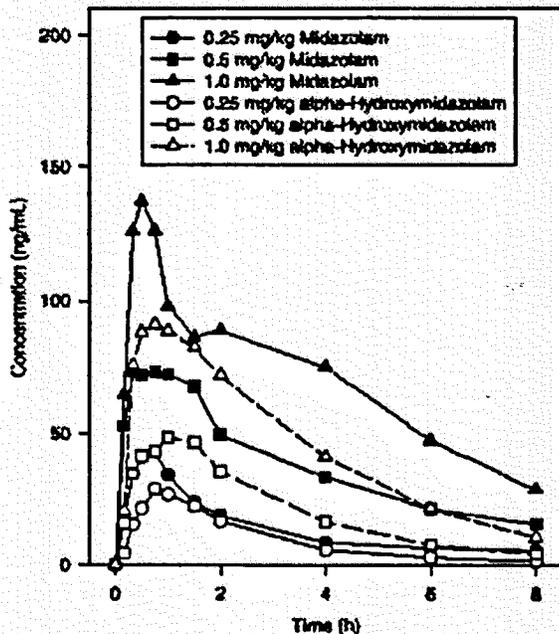


Figure 2. Mean plasma concentration versus time profile of midazolam and α -hydroxymidazolam following oral administration of 0.25, 0.50, 1.0 mg/kg of Versed syrup in pediatric patients of age 6 months to <16 years old (protocol NR 15323).

Table 3. Pharmacokinetic parameters for midazolam (mean \pm SD) following a single oral dose of 0.25, 0.50, or 1.0 mg/kg of midazolam (protocol NR15323).

Number of Subjects/Age Group	Dose	T _{max} (h)	C _{max} (ng/mL)	AUC _{0-∞} (ng.h/mL)	T _{1/2} (h)
6 months to <2 years					
1	0.25	0.17	28.0	67.6	5.82
1	0.50	0.35	66.0	152.0	2.22
1	1.00	0.17	61.2	224.4	2.97
2 to <12 years					
18	0.25	0.72 \pm 0.44	63.0 \pm 30.0	138.0 \pm 89.5	3.16 \pm 1.50
18	0.50	0.95 \pm 0.53	125.6 \pm 75.8	306.1 \pm 195.8	2.71 \pm 1.09
18	1.00	0.88 \pm 0.99	201.0 \pm 101.	742.7 \pm 642.1	2.37 \pm 0.96
12 to <16 years					
4	0.25	2.09 \pm 1.35	29.1 \pm 8.2	154.7 \pm 84.6*	6.83 \pm 3.84*
4	0.50	2.65 \pm 1.58	117.9 \pm 8.2	820.8 \pm 567.7*	4.35 \pm 3.31*
2	1.00	0.55 \pm 0.28	190.5 \pm 47.4	565.8 \pm 15.7	2.51 \pm 0.18

* n=3 (for one subject each in the dose groups of 0.25 and 0.5 mg/kg, there was no apparent log-linear decline)

Table 4. Pharmacokinetic parameters for α -hydroxymidazolam (mean \pm SD) for following a single oral dose of 0.25, 0.50, or 1.0 mg/kg of midazolam (protocol NR15323).

Number of Subjects/Age Group	Dose	T _{max} (h)	C _{max} (ng/mL)	AUC _{0-∞} (ng.h/mL)	T _{1/2} (h)	AUC _M /AUC _P
6 months to <2 years						
1	0.25	0.72	12.3	26.7	1.05	0.38
1	0.50	1.02	45.4	103.1	1.60	0.65
1	1.00	0.17	32.2	101.3	2.37	0.43
2 to <12 years						
18	0.25	0.92 \pm 0.43	40.5 \pm 19.4	87.7 \pm 31.7	2.16 \pm 0.90	0.75 \pm 0.33
18	0.50	1.15 \pm 0.53	75.6 \pm 44.2	179.4 \pm 81.0	2.14 \pm 0.74	0.67 \pm 0.28
18	1.00	1.26 \pm 1.18	139.7 \pm 59.8	423.4 \pm 229.6	1.81 \pm 0.67	0.71 \pm 0.32
12 to <16 years						
4	0.25	2.38 \pm 1.10	19.5 \pm 7.0	74.8 \pm 16.5	3.98 \pm 1.93	0.49 \pm 0.21
4	0.50	2.78 \pm 1.41	71.0 \pm 78.0	264.8 \pm 125.8	2.60 \pm 1.02	0.41 \pm 0.23
2	1.00	0.55 \pm 0.28	190.2 \pm 13.3	370.9 \pm 50.8	1.75 \pm 0.37	0.63 \pm 0.10

6.1.1 DOSE-PROPORTIONALITY WITHIN THE AGE GROUPS

The age group of 6 months to <2 years had only one patient at each of the doses and therefore no rigorous dose-proportionality assessment could be made across the doses in this age group. In the age group 2 to <12 years, the mean dose-normalized C_{max} showed a decreasing trend, however it was not statistically significant. The dose-normalized AUC_{0-∞} showed a non statistically significant increase with increasing doses. In the age group 12 to <16 years, the mean dose-normalized C_{max} was not statistically significantly different across the three doses while the dose-normalized AUC_{0-∞} for the 0.5 mg/kg group was significantly higher. However, because of the small patient numbers, this statistical analysis may be meaningless.

In the age group 6 months to <2 years, there is only one patient each in the three dose groups precluding any concrete analysis on α -hydroxymidazolam pharmacokinetics. In the age group 2 years to < 12 years (54 patients), the mean ratios of the AUC_{0-∞} of α -hydroxymidazolam to the AUC_{0-∞} of midazolam were fairly constant ranging from 0.67 to 0.75, regardless of the dose group. Similarly, in the age group 12 years to < 16 years, the mean ratios of the AUC_{0-∞} of α -hydroxymidazolam to the AUC_{0-∞} of midazolam were fairly constant ranging from 0.41 to 0.63. These data suggest that patients 2 to <12 years old have a slightly higher metabolic capacity or slower clearance of α -hydroxymidazolam than patients 12 to <16 years old. (However, mean dose-normalized AUC's of midazolam ranged from 24.5 to 27.2 ng.hour/mL in group 2 compared to 11.8 to 22.5 ng.hour/mL in group 3 precluding any concrete conclusions from the above data). Published studies in adults (43, 48, 51, 59, 60, 68) report mean ratios of the AUC_{0-∞} of α -hydroxymidazolam to the AUC_{0-∞} of midazolam in the range of 0.40 to 0.56 which is smaller than the 0.41-0.75 range seen in pediatrics in the current study.

6.1.2 DOSE-PROPORTIONALITY ACROSS THE AGE GROUPS

ANOVA was performed on dose-normalized C_{max} and dose-normalized $AUC_{0-\infty}$ among the three dose-groups independent of age group. No statistically significant difference was found for the mean values (Table 5) indicating dose-proportionality in the range of 0.25 mg/kg to 1.0 mg/kg across the age groups. However, a small trend towards increase in the dose-normalized $AUC_{0-\infty}$ can be seen with increase in dose.

Table 5. Mean dose-normalized pharmacokinetic parameters for midazolam.

Parameter	Dose Group 0.25 mg/kg	Dose Group 0.5 mg/kg	Dose Group 1.0 mg/kg
Dose-Normalized C_{max}	0.01085 ± 0.00757	0.01096 ± 0.01073	0.00831 ± 0.00469
Dose-Normalized $AUC_{0-\infty}$	0.02311 ± 0.01130	0.02566 ± 0.0140	0.02689 ± 0.01848

6.1.3 SEDATION

Mean and 95% confidence intervals for midazolam concentration and the sum of midazolam and α -hydroxymidazolam concentration versus sedation, ease of separation from parent and at mask induction with the inhalation anesthetic scores are presented in Table 6. Figure 3 displays the trend that is seen between sedation score and midazolam concentration or the sum of midazolam and α -hydroxymidazolam concentration (higher concentrations resulted in higher sedation scores). ANOVA analysis indicated that the mean midazolam concentration and the mean of the sum of midazolam and α -hydroxymidazolam concentration for those patients with a sedation score of 4 is significantly different than the mean concentration for those patients with a sedation score of 3 or 2. A statistically significant difference was also found between the mean concentrations for sedation score 3 and 2.

Comparative analysis suggests that there is an association between dose and sedation, with a higher proportion of patients in the 1.0 mg/kg treatment group having a satisfactory sedation response. Overall, 69/85 (81%) patients had satisfactory sedation post-treatment: 18/28 (64%) patients in the 0.25 mg/kg treatment group, 20/24 (83%) in the 0.50 mg/kg group, and 31/33 (94%) patients in the 1.0 mg/kg treatment group.

The onset time to satisfactory sedation for patients with an unsatisfactory sedation rating at baseline, occurred within 20 minutes for 48/81 (59%) patients: 11/26 (42%) patients in the 0.25 mg/kg treatment group, 14/24 (58%) patients in the 0.50 mg/kg treatment group, and 23/31 (74%) patients in the 1.0 mg/kg treatment group.

6.1.4 ANXIOLYSIS

No trend was observed between at mask induction scores or scores at separation from parents and midazolam concentration or the sum of midazolam and α -hydroxymidazolam concentration (Table 6). Anxiolysis is a more variable surrogate measurement of clinical response. In this population, older children, due to their better understanding of a procedure tend to be less anxious than younger patients. Therefore, an anxiolytic effect may be more difficult to demonstrate in this age group.

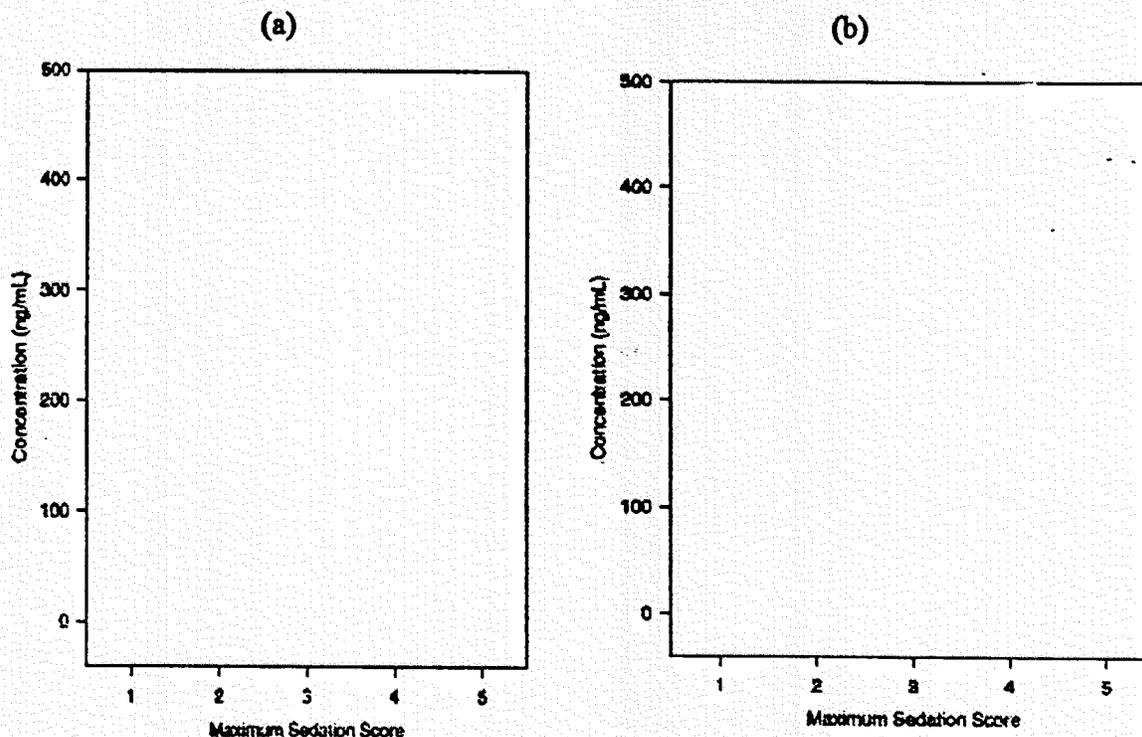


Figure 3. Plot of midazolam concentration (a) and combined midazolam and α -hydroxymidazolam concentration (b) versus maximum sedation score.

Table 6. Mean concentrations (and 95% confidence intervals for sedation scores) of midazolam and midazolam plus α -hydroxymidazolam versus maximum sedation score, anxiolysis score at time of separation from parents, and time of mask induction in pediatric patients (protocol 15323).

Sedation	Score 1	Score 2 (Awake/Calm)	Score 3 (Drowsy)	Score 4 (Asleep)
$C_{\text{midazolam}}$, ng/mL	-	8.26 (0.40-16.12)	67.16 (45.00-89.32)	160.57 (75.16-245.98)
$C_{\text{midazolam} + \alpha\text{-hydroxymidazolam}}$, ng/mL	-	10.03 (0.07-19.98)	92.44 (61.66-123.21)	264.34 (142.16-386.52)
Separation From Parents	Score 1 (Poor)	Score 2 (Fair)	Score 3 (Good)	Score 4 (Excellent)
$C_{\text{midazolam}}$, ng/mL	72.00	104.83	82.19	77.23
$C_{\text{midazolam} + \alpha\text{-hydroxymidazolam}}$, ng/mL	107.07	173.61	145.50	120.87
Mask Induction	Score 1 (Poor)	Score 2 (Fair)	Score 3 (Good)	Score 4 (Excellent)
$C_{\text{midazolam}}$, ng/mL	82.00	-	65.51	87.03
$C_{\text{midazolam} + \alpha\text{-hydroxymidazolam}}$, ng/mL	122.03	-	123.42	142.82

6.1.5 TASTE TEST

Overall, taste acceptability was considered satisfactory (accepted readily or with grimace or with a complaint) in 83 of 84 patients. Only one patient in the 2 to <12 years age group rejected it entirely.

6.2 ABSOLUTE BIOAVAILABILITY (ARM II)

This was a two-way randomized cross-over study. The absolute bioavailability was estimated in 6 out of 10 pharmacokinetically evaluable patients who completed both IV and PO doses (3 patients each in the 6 months to <2 year age group and 2 to <12 year age group, respectively). Patients received 0.50 mg/kg oral dose and 0.15 mg/kg IV dose. The mean value for absolute bioavailability across all ages was 35.8% with a standard deviation of 24.4% and range of 8.6 to 71.1%. Published values of the mean absolute bioavailability of midazolam administered as a solution or tablet in adults in the dose range of 0.1 mg/kg to 0.41 mg/kg ranged from 24 to 49%.

In order to obtain a more complete description of the relationship between absolute bioavailability and age, the data from 67 patients who received oral midazolam syrup in arm I was combined with other patients who received intravenous midazolam in arms II and III and other historical data. NONMEM analysis was conducted using this data. The absolute bioavailability estimated by this approach was 37% with 95% confidence intervals of 29% to 44%. Age or weight were statistically significant covariates. However, age and weight were highly correlated. With age as a covariate, the total systemic clearance of midazolam increased modestly with increasing body weight of the patient. The absolute bioavailability was not found to vary with pediatric age.

6.3 INTRAVENOUS PHARMACOKINETICS (ARM III)

This was an open-label, age-stratified study in which 16 patients received a single intravenous 0.15 mg/kg midazolam dose. No efficacy measures were obtained in this arm. Data from 6 patients in the absolute bioavailability arm who received IV dose of 0.15 mg/kg were also included in this evaluation.

Table 7. Pharmacokinetic parameters for midazolam (mean \pm SD) following a single IV dose of 0.15 mg/kg of midazolam (protocol NR15323).

Age Group	Number of Patients	T _{1/2} (h)	AUC _{0-∞} (ng·h/mL)	Vd _{ss} (L/kg)	Vd _β (L/kg)	CL (mL/min/kg)
6 months to <2 years	5	2.9 \pm 2.2	282 \pm 153	1.24 \pm 0.27	2.17 \pm 0.53	11 \pm 6.3
2 to <12 years	13	3.0 \pm 1.7	281 \pm 102	1.32 \pm 0.67	2.49 \pm 1.42	10 \pm 3.8
12 to <16 years	2	4.5 \pm 0.01	294 \pm 122	2.02 \pm 0.73	3.61 \pm 1.51	9.3 \pm 3.8

Table 8. Pharmacokinetic parameters (mean±SD) for α -hydroxymidazolam following a single IV dose of 0.15 mg/kg of midazolam (protocol NR15323).

Age Group	Number of Patients	T _{max} (h)	C _{max} (ng/mL)	AUC _{0-∞} (ng.h/mL)	T _{1/2} (h)	AUC _M /AUC _P
6 months to <2 years	5	0.28±0.15	32.5±25.8	48.1±10.8	3.18±2.4	0.21±0.11
2 to <12 years	13	0.45±0.48	32.3±18.5	69.2±29.6	2.29±0.9	0.23±0.14
12 to <16 years	2	0.91±0.91	53.5±53.0	128.0±91.4	2.76±0.5	0.39±0.14

The mean pharmacokinetic parameters of midazolam and α -hydroxymidazolam as a function of age are presented in Tables 7 & 8. Comparison between the three age groups is complicated as the 12 to <16 years old group consisted of two patients only. Between the three age groups- 6 months to <2 years old and 2 to <12 years old had similar midazolam pharmacokinetic parameter values. The 12 to <16 years old group tended to differ from the younger groups with slightly smaller clearance, a higher volume of distribution, and a longer terminal half-life. Because of the small sample size of two patients in this age group, no definite conclusions can be made regarding the age dependent pharmacokinetics of midazolam. However, a small trend towards a decrease in clearance with age is seen across the age groups. Overall, the clearance values ranged from 9.3 to 11 mL/min/kg, the terminal half-life ranged from 2.9 to 4.5 hours, and the steady state volume of distribution ranged from 1.24 to 2.02 L/kg.

Published studies evaluating IV midazolam in adults in doses ranging from 0.03 mg/kg to 0.81 mg/kg, report mean clearance values in the range of 4.0 to 12.4 mL/min/kg, mean steady state volume of distribution values in the range of 0.68 to 1.1 L/kg and mean terminal half-life values in the range of 1.1 to 3.5 hours (2, 23, 24, 27, 43, 45, 47, 48, 50, 51, 52, 53, 54, 57, 60, 87). However, a plot of clearance versus dose from data in the above referenced studies showed a tendency towards decreasing clearance with increasing dosage. At a dose of 0.15 mg/kg (i.e., at the dose used in protocol 15323), adult mean clearance values ranged from 4.6 to 6.1 mL/min/kg, mean values of steady state volume of distribution ranged from 0.72 to 1.05 L/kg, and mean values of terminal half-life ranged from 2.2 to 2.3 hours (24, 53). Therefore at comparative doses, it appears as if adults have a smaller clearance, smaller volume of distribution and shorter terminal half-life.

The mean AUC_{0-∞} ratio values of AUC_{0-∞} of α -hydroxymidazolam to midazolam were similar between the age groups of 6 months to <2 years and 2 to <12 years while it was higher in the 12 to <16 years group. The mean values ranged from 0.21 to 0.39 across the age groups. Published AUC_{0-∞} ratio values of α -hydroxymidazolam to midazolam was smaller (about half) in adults (mean values ranged from 0.12 to 0.14) compared to the values obtained for children in this study.

It should be noted that in the clinical study 15323, patients were stratified into groups of 6 months to <2 years, 2 years to <6 years, and 6 years to <16 years. In order to find out if there is any trend in the pharmacokinetics according to this age classification, this reviewer reanalyzed the IV data and oral data (presented in arm I) by reclassifying the original data in the age groups of 2 years to <12 years and 12 years to <16 years into the age groups of 2 years to <6

years and 6 years to <16 years. The IV data is shown in Table 9. The oral data (0.5 mg/kg dose only) is presented in Table 10. It can be seen from these tables that there are no dramatic differences in the mean clearance and terminal half-life values after IV dose or in the dose-normalized AUC values after oral dose between the two groups of 2 to < 6 years and 6 to < 16 years. This has implications on the dosing recommendations made by the sponsor. Sponsor recommends that the younger group of 6 months to < 6 years of age may require a higher than usual dose up to 1.0 mg/kg. The pharmacokinetic data shown in Tables 9-10, does not show a higher clearance in the age group of 2 to <6 years (if anything, clearance is slightly lower) compared to the 6 to < 16 years of age group and therefore does not support the higher dose requirement in the age group of 2 to < 6 years.

Table 9. Mean clearance and terminal half-life values for midazolam following a single IV dose of 0.15 mg/kg of midazolam after reclassification of the age groups (protocol NR15323).

Parameter	2 to < 6 years (n=9)	6 to < 16 years (n=6)
CL, Lit/hr/kg	0.588	0.605
T1/2, hr	3.0	3.51

Table 10. Mean dose-normalized values for midazolam following a single oral dose of 0.50 mg/kg of midazolam after reclassification of the age groups (protocol NR15323).

Parameter	2 to < 6 years (n=8)	6 to < 16 years (n=10)
AUC/dose, ($\mu\text{g}\cdot\text{hr}/\text{Lit}$)/ μg	30.45	24.1

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pages of trade

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information

Labeling notes: Labeling information on the food effect information from this study should be inserted into the absorption sub-section of the pharmacokinetics section of the package insert as follows;

7.2 DRUG-DRUG INTERACTIONS

All of the studies summarized in this section were extracted from published articles. These studies were conducted in healthy adult subjects. No drug-drug interactions studies have been conducted in pediatric patients by the sponsor using versed® oral syrup.

Midazolam is primarily oxidized to a pharmacologically active metabolite, α -hydroxymidazolam, via cytochrome P450III_{A4} mediated metabolism. Due to the presence of this metabolite, the relationship between plasma drug concentrations and drug effects becomes more complex after the oral administration of midazolam where the metabolite levels are relatively high compared to parenteral routes of administration. None of the studies summarized below evaluated the effect of other drugs on the formation and elimination of α -hydroxymidazolam making dose-adjustment recommendations for oral midazolam difficult. When midazolam is administered with inducers (drugs that increase the first-pass metabolism of midazolam), the plasma concentrations of midazolam are lower but ratio of α -hydroxymidazolam to midazolam C_{max} and AUC is expected to be higher. When midazolam is administered with inhibitors (drugs that decrease the first-pass metabolism of midazolam), the plasma concentrations of midazolam are higher but the ratio of α -hydroxymidazolam to midazolam C_{max} and AUC values is expected to be lower. Because of these opposing effects on midazolam and α -hydroxymidazolam plasma concentrations, the clinical consequences of metabolic drug-drug interactions cannot be predicted from pharmacokinetic studies unless substantial changes are observed. While an increased terminal elimination half-life may extend the duration of midazolam effects, changes in peak plasma concentration (C_{max}) have a greater influence on the onset and intensity of midazolam's clinical effects.

7.2.1 EFFECT OF INDUCERS OF DRUG METABOLISM ON MIDAZOLAM PHARMACOKINETICS

Data from published articles showed that inducers of CYP3A4, including rifampin, carbamazepine, and phenytoin, markedly decreased (>90%) the C_{max} and AUC, and pharmacologic effects (Digit symbol substitution test, critical flicker fusion test, standard pupil diameter, Maddox wing test, and drowsiness) of oral midazolam (65,101). Although, the effect of phenobarbital has not been examined, it is also expected to have a similar effect of other inducers. Therefore, wherever possible these drugs should be avoided in patients receiving midazolam.

7.2.2 DRUGS THAT DO NOT AFFECT THE PHARMACOKINETICS OF MIDAZOLAM

The results from the literature also indicated that many drugs from different therapeutic categories when administered concurrently did not affect the pharmacokinetics and/or pharmacodynamics of oral midazolam. Terbinafine (250 mg/day), nitrendipine, azithromycin, and antacids (magnesium trisilicate and magnesium hydroxide 30 mL/7 times a day) did not affect the pharmacokinetics of oral midazolam.

7.2.3 EFFECT OF INHIBITORS OF DRUG METABOLISM ON MIDAZOLAM PHARMACOKINETICS

All of the studies summarized in this section (except where noted) were conducted with oral midazolam using adult volunteers. Table 12 shows that erythromycin, fluconazole, ketoconazole, itraconazole, diltiazem, and verapamil may cause clinically significant interaction with oral midazolam. The effect of these drugs on the pharmacokinetics of α -hydroxymidazolam after midazolam administration were not examined. Erythromycin, diltiazem, verapamil, itraconazole, ketoconazole, and fluconazole markedly increased midazolam C_{max} and AUC and pharmacologic effect (surrogate CNS effects) of oral midazolam. The intensity and duration of midazolam effects may be significantly increased upon coadministration with these drugs. If the administration of these drugs cannot be avoided, then a reduction in the dosage of midazolam is warranted. In particular, ketoconazole and itraconazole show striking increases in C_{max} and AUC values (62). A full copy of this article is attached in appendix III at the end of the list of references. There was a 309% and 1490% increase in C_{max} and AUC respectively of midazolam after the administration of 400 mg/day ketoconazole. Coadministration of 200 mg/day itraconazole resulted in a 240% and 980% increase in C_{max} and AUC respectively of midazolam. Volunteers participating in this study could hardly be awakened during the first hour after administration and most experienced amnesia lasting for several hours. These drugs should be avoided in pediatric patients receiving midazolam. Moderate increases in the C_{max} and AUC values were also seen upon concurrent administration of grapefruit juice, cimetidine, and ranitidine as well. Grapefruit juice, especially poses an interesting problem in that it is possible that the pediatric patients are given grapefruit juice to wash down the Versed[®] syrup. Pre-treatment with 200 mL of grapefruit juice one hour before the administration of 15 mg oral midazolam resulted in a 56% and 52% increase in C_{max} and AUC of midazolam (110). Therefore, labeling instructions should specifically mention that grapefruit juice be not given to these patients when they are administered Versed[®] syrup.

Table 12. Effect of inhibitors of drug metabolism on orally administered midazolam.

Interacting Drug	Dose	% Increase in C_{max}	% Increase in AUC	Change in effect	Reference
Azithromycin	500 mg qd	29	27	No increase	104
Erythromycin	500 mg tid	170	341	Marked increase	63
Erythromycin	500 mg tid	171	281	Marked increase	106
Roxithromycin	300 mg/day	37	47	Slight increase	66
Diltiazem	60 mg tid	105	275	Marked increase	67
Verapamil	80 mg tid	97	192	Marked increase	67
Itraconazole	100 mg/day	156	474	Marked increase	61
Itraconazole	200 mg/day	240	980	Marked increase	62
Itraconazole	200 mg/day	80	240	Marked increase	107
Ketoconazole	400 mg/day	309	1490	Marked increase	62
Fluconazole	200 mg/day	150	250	Marked increase	107
Magnesium Trisilicate	30 mL of BP	13	37	Not tested	105
Magnesium Hydroxide	30 mL 7 times/day	18	-3	No increase	44
Ranitidine	150 mg tid	50	66	slight increase	108
Ranitidine	150 mg bid	15	23	Not tested	53
Ranitidine	150 mg bid	30	12	Not tested	47
Ranitidine	150 mg bid	52	66	Not tested	105
Ranitidine	150 mg tid	67	39	Slight increase	44
Ranitidine	300 mg	NA	9	none	109
Cimetidine	400 mg bid	25	35	Not tested	53
Cimetidine	300 mg qid	6	-10	Not tested	47
Cimetidine	200 mg tid	138	102	Not tested	105
Cimetidine	400 mg nocte				
Cimetidine	400 mg tid	60	37	Slight increase	44
Cimetidine	800 mg	NA	26	Slight increase	109
Grapefruit Juice	200 mL	56	52	Increased	110

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Note: Section 10 (proposed package insert) of this review has comprehensive information on drug-drug interaction aspects in appropriate sections of the package insert.

7.3 RENAL IMPAIRMENT

In renal impairment, α -hydroxymidazolam can be expected to accumulate prolonging the pharmacological effects of midazolam. Unfortunately, in the published study that evaluated the pharmacokinetics of midazolam in chronic renal failure patients, α -hydroxymidazolam pharmacokinetics were not evaluated (41). Chronic renal failure patients (n=14) had a significantly higher plasma free drug fraction (6.5%) compared with that (3.9%) in healthy volunteers (n=14). Although the total clearance and volume of distribution of total (bound plus unbound) midazolam in patients with chronic renal failure were higher than those of subjects with normal renal function, there were no alterations in the volume of distribution or clearance of unbound drug in the renal failure patients (elimination half-life was the same in both groups). Therefore, based on midazolam's pharmacokinetics alone, there does not appear to be a need to change the dose of midazolam. However, since the accumulation potential of α -hydroxymidazolam is likely but unknown, it should be titrated for the desired effect in patients with chronic renal disease.

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7.4 HEPATIC DYSFUNCTION

Chronic hepatic disease alters the pharmacokinetics of midazolam. Following IV administration of 0.075 mg/kg midazolam, the clearance of midazolam was reduced by about 50%, and the elimination half-life was increased by about 100% in patients (n=7) with severe alcoholic cirrhosis compared with subjects (n=8) having normal hepatic function (98). In another study, following iv administration of 7.5 mg of midazolam, the clearance of midazolam was reduced by about 40% and the elimination half-life was increased by about 90% in patients (n=7) with cirrhosis versus subjects (n=7) with normal liver function (99). In the same patients with cirrhosis, following oral administration of 15 mg of midazolam, C_{max} and bioavailability values were 43% and 100% higher, respectively, in patients with liver disease than in subjects with normal liver function. A copy of this article (reference 99) is attached in appendix III at the end of the list of references.

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7.5 EFFECTS OF AGE, GENDER, AND OBESITY ON PHARMACOKINETICS

The effect of age, gender, and obesity on the pharmacokinetics of 2.5 to 5.0 mg IV and 5 to 10 mg oral doses of midazolam were studied in young elderly male and female subjects as well as young obese subjects. The terminal half-life after IV administration was prolonged in the elderly (60 to 74 years) compared to young male subjects (5.6 versus 2.1 hours), and clearance was reduced (4.4 versus 7.8 mL/min/kg). The bioavailability was higher (50% versus 41%) in the elderly compared with young males. However, the apparent volume of distribution based on the elimination phase, $Vd\beta$ and the unbound fraction were not different between these two groups. The pharmacokinetics of midazolam in elderly (60 to 74 years old) compared to young (24 to 33 years old) female subjects were not different. Between obese subjects and normal body weight subjects, the $Vd\beta$ (1.7 versus 2.7 L/kg) and terminal half-life (2.7 versus 8.4 hour) are significantly larger in obese subjects, but clearance and bioavailability were not different between the two groups.

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8. CONCLUSIONS

I. Protocol 15323:

Oral pharmacokinetics in pediatrics

1. Midazolam exhibits dose-proportionality between oral doses of 0.25 to 1.0 mg/kg within the age groups of 2 years to <12 years. Small sample size did not permit meaningful assessment of dose-proportionality in the age groups of 6 months to <2 years and 12 years to <16 years.
2. Midazolam exhibits dose-proportionality between oral doses of 0.25 to 1.0 mg/kg in pediatric patients across the age groups of 6 months to 16 years.
3. The absolute bioavailability of 0.5 mg/kg oral dose of midazolam in pediatric patients is about 36%. It does not seem to vary in the age range of 6 months to 16 years.
4. The $AUC_{0-\infty}$ ratio of α -hydroxymidazolam to midazolam for the oral dose is higher in pediatric patients than in adults.
5. No definite trend in age dependent pharmacokinetics of midazolam and α -hydroxymidazolam after oral doses of 0.25, 0.5, and 1.0 mg/kg midazolam across the three age groups was seen. Perhaps, the small number of patients in group 6 months to <2 years (three at each dose group) and in group 12 years to < 16 years (three evaluable patients each at doses of 0.25 mg/kg and 0.5 mg/kg and two patients at 1.0 mg/kg dose) may have contributed to this by weighting the data towards the group 2 years to < 12 years that had the majority of patients.
6. A trend between sedation scores and midazolam concentrations or combined midazolam plus α -hydroxymidazolam concentration in pediatric patients was seen in the age group of 6 months to 16 years administered 0.25, 0.5, and 1.0 mg/kg doses of Versed[®] syrup. The higher the midazolam or combined midazolam plus α -hydroxymidazolam concentration, the greater the maximum sedation score for patients. Mean midazolam concentrations of

- 8.3, 67.2, and 160.9 ng/mL or mean midazolam plus α -hydroxymidazolam concentrations of 10.0, 92.4, and 264.3 ng/mL resulted in sedation scores of 2 (awake/calm), 3 (drowsy), and 4 (asleep) respectively.
7. Results from protocol 15323 show no trend between midazolam or midazolam plus α -hydroxymidazolam concentration and anxiolysis scores in the pediatric patients in the age group of 6 months to 16 years.

Intravenous pharmacokinetics in pediatrics

8. In the age group of 6 months to <16 years, the clearance values ranged from mL/min/kg, the terminal half-life ranged from hours, and the steady state volume of distribution ranged from L/kg.
9. The pharmacokinetics of midazolam were similar in the age groups of 6 months to <2 years and 2 years to <12 years. Insufficient sample size does not permit drawing definite conclusions about the age group of 12 years to <16 years. A small trend towards decreasing clearance was seen across the three age groups from 6 months to <16 years. However, because the age group of 12 years to <16 years had only 2 patients no definite conclusions can be drawn regarding this trend.
10. At comparative doses of 0.15 mg/kg IV midazolam dose, the clearance values appear to be smaller (about 2 fold) in adults compared to pediatrics in the age group of 6 months to <16 years.
11. The $AUC_{0-\infty}$ ratio of α -hydroxymidazolam to midazolam is higher in pediatrics (about 2 fold) in the age range of 6 months to <16 years over that in adults after an IV dose.
12. Pharmacokinetic data suggests that a dose of 0.25 mg/kg may be optimum in pediatric patients. Pharmacokinetic data also suggests that pediatric patients in the age range of 6 months to < 6 years may not need a higher dose of 1.0 mg/kg. Dose of 0.25mg/kg is likely to be efficacious in the entire age range of 6 months to <16 years.

II. Results from published articles:

13. A number of published studies, conducted with adult subjects, using effect compartment PK/PD modeling (sigmoidal E_{max} model), consistently demonstrated a strong correlation between plasma midazolam concentrations and surrogate CNS effects (EEG, digit symbol substitution test, reaction time, tracing errors, saccadic eye movement, visual evoked response, drowsiness etc.) in doses ranging from 0.03 mg/kg to 0.15 mg/kg IV.
14. Data summarized from published studies in adults indicates that midazolam undergoes oxidative metabolism mediated by cytochrome P450 IIIA4 isozyme to a major and active metabolite, α -hydroxymidazolam.
15. α -Hydroxymidazolam was reported to be equipotent to midazolam.
16. Binding of midazolam and α -hydroxymidazolam to plasma albumin is about 96.5% and 89.4% respectively.
17. Published studies on drug-drug interactions in adults indicate that CYP IIIA4 inducers such as rifampin and carbamazepine decreased the C_{max} and AUC of orally administered midazolam by about 95% while CYP IIIA4 inhibitors such as erythromycin, diltiazem, verapamil, ranitidine, cimetidine, itraconazole, fluconazole, and ketoconazole markedly

increased the C_{max} and AUC of orally administered midazolam. The increases in C_{max} and AUC, respectively, of midazolam were, 170% and 341% with erythromycin, 105% and 275% with diltiazem, 97% and 192% with verapamil, 240% and 980% with itraconazole, 150% and 250% with fluconazole, and 309% and 1490% with ketoconazole. Pretreatment with grapefruit juice was reported to result in a 56% and 52% increase in C_{max} and AUC, respectively, of oral midazolam.

18. Published studies in hepatic failure patients indicate that chronic hepatic disease alters the pharmacokinetics of midazolam. Following IV administration, the clearance of midazolam was reported to be reduced by about 40-50%, and the elimination half-life was increased by about 90-100% in patients with alcoholic cirrhosis compared with subjects having normal hepatic function. After oral administration, C_{max} and bioavailability were reported to be increased by about 43% and 100% respectively.
19. Although the pharmacokinetics of intravenous midazolam in patients with chronic renal failure differed from those of subjects with normal renal function, there were no alterations in the distribution, elimination, or clearance of unbound drug in the renal failure patients. However, the accumulation potential of the major and active metabolite α -hydroxymidazolam which is primarily excreted in the urine as a glucuronide is unknown.

9. GENERAL COMMENTS (not to be sent to the sponsor)

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**APPENDIX I
STUDY SUMMARY OF PROTOCOL 15323**

NDA:20-942

SUBMISSION DATE: February 4, 1998

VOLUME: 10-18

INVESTIGATOR(S)/INSTITUTION

STUDY DESIGN

All three arms were multicenter and age stratified (6 months to <2years, 2 to <12 years, and 12 to <16 years) including both in-patient and out-patient pediatric patients requiring a sedative for day-stay or minor procedures. Arm I was randomized, observer blind, parallel group; Arm II was two-way crossover, open-label and had a minimum of 24 hour washout period; Arm III was open-label.

SUBJECT DEMOGRAPHICS

(1) Number of subjects-

	<u>Enrolled</u>	<u>Evaluable for</u>			<u>Discontinued</u>		
		PK	PD	Safety	AEs	Death	Other
Arm I	85	67	85	85	0	0	18
Arm II	10	6	0	10	0	0	3
Arm III	16	14	0	16	0	0	2
Total	111	87	85	111	0	0	23

(2) Demographics-

	Arm I	Arm II	Arm III
Number	85	10	16
Sex (M/F)	51/34	5/5	7/9
Weight (kg)Mean	29.1	16.0	23.3
± SD	±17.8	±8.1	±16.3

ANALYTICAL METHODOLOGY

PHARMACODYNAMIC EFFECTS AND TASTE ASSESSMENT

Sedation and Anxiolysis scores (Arm I only):

Sedation; Baseline and at 10-minute intervals up to 30 minutes after dosing. Sedation was assessed according to the following scale (scores of 1 and 2 were considered unsatisfactory while a score of 3 or higher was considered satisfactory)-

1. *Alert/Active*: Moving, agitated, not calm, physical or verbal display of apprehension.
2. *Awake/Calm*: Not drowsy, responds to name/commands spoken in normal tone.
3. *Drowsy*: Relaxed, quiet, responds readily to name/commands spoken loudly or repeatedly, cooperative.
4. *Asleep*: Does not respond readily to name/commands spoken loudly or repeatedly but responds to mild shaking or prodding.
5. *Asleep*: Does not respond readily to name/commands spoken loudly or repeatedly or mild shaking or prodding.

Anxiolysis; Baseline and at separation from parents and mask induction with nitrous oxide. Anxiolysis was assessed according to the following scale-

1. *Poor*: Afraid, combative crying.
2. *Fair*: Fearful, moderate expressions of fear, not combative.
3. *Good*: Slightly fearful, easily calmed.
4. *Excellent*: Unafraid, cooperative calm.

Taste Test: Acceptability of the oral syrup formulation was evaluated in Arm I of the study. The patient was assessed by facial expressions and manner of acceptance for acceptability of the oral syrup as follows ;

- Accepted readily
- Accepted with grimace
- Accepted with verbal complaint
- Rejected entirely, spit out.

Redacted

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pages of trade

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APPENDIX III

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Reference 43

Pharmacokinetic-pharmacodynamic modeling of the central nervous system effects of midazolam and its main metabolite α -hydroxymidazolam in healthy volunteers

The pharmacodynamics of midazolam and its main metabolite α -hydroxymidazolam were characterized in individual subjects by use of saccadic eye movement and electroencephalographic (EEG) effect measurements. Eight healthy volunteers received 0.1 mg/kg midazolam intravenously in 15 minutes, 0.15 mg/kg α -hydroxymidazolam intravenously in 15 minutes, 7.5 mg midazolam orally and placebo in a randomized, double-blind, four-way crossover experiment. Plasma concentrations of midazolam, α -hydroxymidazolam and 4-hydroxymidazolam were measured by gas chromatography. The amplitudes in the 11.5 to 30 Hz (beta) frequency band were used as EEG effect measure. The concentration-effect relationships were quantified by the sigmoid maximum effect model. The median effective concentrations of midazolam and α -hydroxymidazolam were (mean \pm SE) 77 ± 15 and 98 ± 17 ng/ml, respectively, for the EEG effect measure. For peak saccadic velocity the values were 40 ± 7 ng/ml for midazolam and 49 ± 10 ng/ml for α -hydroxymidazolam. The maximum effect values were similar for both compounds. The effects observed after oral administration of midazolam could not be predicted accurately by an additive and competitive interaction model. It seems that α -hydroxymidazolam is highly potent with respect to the measured effects and contributes significantly to those effects of midazolam after oral administration. (*CLIN PHARMACOL THER* 1992;51:715-28.)

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Benzodiazepines are widely used in clinical practice because of their anxiolytic, muscle relaxant, anticonvulsant, and sedative-hypnotic effects. Appropriate measures of clinically relevant drug effects are required to elucidate the relationships between pharmacokinetics and pharmacodynamics of benzodiazepines. Recently, quantitative electroencephalographic (EEG) effect parameters have been used to characterize the

concentration-effect relationships of benzodiazepines by appropriate pharmacodynamic models.^{1,2} The formation of pharmacologically active metabolites may complicate the characterization of pharmacokinetic-pharmacodynamic relationships. Most benzodiazepines have metabolites with affinity for the benzodiazepine receptor.³⁻⁹ However, little is known about the in vivo potency and intrinsic efficacy of these metabolites, their interaction with the parent compound, and their contribution to the pharmacologic effects.

The possibility that metabolites contribute to the central nervous system effects of midazolam should be considered. Midazolam is rapidly eliminated from the body by metabolism to two substances, α -hydroxymidazolam and 4-hydroxymidazolam, which are both pharmacologically active.¹⁰⁻¹² Both metabolites are rapidly conjugated by glucuronic acid to form an inactive product.¹¹ After intravenous administration of

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midazolam, relatively low concentrations of the metabolites are found. However, relatively high concentrations of α -hydroxy-midazolam were observed after oral administration.^{11,13} The concentration-effect relationship of midazolam based on reaction time measurements was shifted to the left after oral administration compared with intravenous administration, suggesting that α -hydroxymidazolam contributed significantly to the central nervous system effects of the parent compound.¹⁴ Also, marked central nervous system effects were observed after intravenous administration of relatively low doses of α -hydroxymidazolam to healthy volunteers.¹² Relationships between plasma concentrations and pharmacologic effect of this metabolite were not derived in these investigations.

The purpose of the present investigation was to mathematically characterize the relationships between plasma concentrations and central nervous system effects of midazolam and α -hydroxymidazolam after intravenous administration of both compounds to healthy volunteers. Effect parameters derived from quantitative EEG analysis and saccadic eye movement measurements were used as measures of drug effect on the central nervous system. The subjects also received midazolam orally to characterize the interaction between the parent drug and its main metabolite.

METHODS

Subjects. The study protocol was approved by the Ethics Review Board of the Leiden University Hospital (Leiden, The Netherlands). Eight healthy non-smoking volunteers (four men and four women) with a mean (\pm SD) age of 22 \pm 1 years and weight of 69 \pm 6 kg were recruited for the study. All volunteers received a full medical examination and all gave written informed consent before participating in the study. The subjects refrained from food and alcohol and caffeine-containing beverages from midnight before the investigation. A light breakfast was served 2 hours after drug administration. The subjects refrained from alcohol and caffeine-containing beverages until the end of the study day.

Study design. The study was a double-blind, double-dummy, four-way crossover experiment randomized according to Latin squares. The subjects each received 0.1 mg/kg midazolam intravenously in 15 minutes, 0.15 mg/kg α -hydroxymidazolam intravenously in 15 minutes, 7.5 mg midazolam orally, or matching placebo at 1-week intervals. The experimental medications were prepared by the Leiden University Hospital Pharmacy. Intravenous midazolam was

prepared from a commercially available solution for intravenous injection (Dormicum, Hoffmann-La Roche, Basel, Switzerland). Solutions of α -hydroxymidazolam for intravenous administration were made available by Hoffmann-La Roche. Oral midazolam was prepared from a commercially available tablet (Dormicum, Hoffmann-La Roche) and administered in a hard gelatin capsule.

After the subjects arrived at the hospital, two intravenous catheters were inserted into both arms of each subject for drug administration and blood sampling, and electrodes for the saccadic eye movement and EEG measurements were applied. Drug effects were frequently measured before and after drug administration. The pharmacodynamic measurement sessions consisted of the following sequence of tests: (1) saccadic eye movements, (2) EEG, (3) blood pressure and heart rate, and (4) EEG. Each sequence took about 4 minutes to complete. Systolic and diastolic blood pressure and heart rate were measured for monitoring purposes by use of an oscillometric blood pressure monitor (MPV 7201, Nihon Kohden, Amsterdam, The Netherlands). Pharmacodynamic testing was performed at 25, 10, and 5 minutes before drug administration for baseline determination and subsequently at 0, 5, 10, 15, 20, 30, 40, 55, 70, 85, 100, 120, 150, 180, 210, 240, and 270 minutes and at 5, 6, 7, and 8 hours after drug administration. For intravenous administration the doses of midazolam and α -hydroxymidazolam were individually adjusted on the basis of the pharmacologic effect measurements. When a subject was unable to perform the saccadic eye movement test because of profound sedation, the intravenous infusion was stopped before 15 minutes. Blood samples were collected into heparinized syringes (Sarstedt monovette, Sarstedt, Nuembrecht, Germany) 10 minutes before drug administration and at 5, 10, 15, 20, 25, 35, 45, 60, 90, 120, and 150 minutes and at 3, 4, 5, 6, and 8 hours after drug intake. Plasma was separated and stored at -40° C until analysis.

Saccadic eye movement measurements. Recording of saccadic eye movements were made by use of a microcomputer-based system for sampling and analysis of eye movements.¹⁵ The details of this method have been described elsewhere.¹⁶ In the present study one session of saccadic stimuli consisted of 12 stepwise displacements of 40 degrees (20 degrees to either side) at intervals varying randomly from 3 to 6 seconds.

EEG measurements. Five silver-silverchloride-cup electrodes were placed on the skull of the subjects at

the positions F_{7c} , F_{7z} , C_7 , P_7 , and O_7 according to the 10-20 international system. Electrode impedance was maintained below 5 k Ω . At specific times before and after drug administration, eight blocks of 8 seconds of EEG were recorded while the subjects were sitting relaxed with their eyes closed. Blocks containing artifacts were excluded from analysis. The subjects were instructed to stay awake during the recording session and were aroused when necessary by verbal stimulation. The subjects were kept awake between the EEG measurements by verbal contact and the eye movement measurements. The EEG signals of two leads, F_7-C_7 and P_7-O_7 , were amplified (Bioelectric amplifier AB-621G, Nihon Kohden) and digitized by use of the CED EEG measurement and analysis system. The low-pass filter was set at 100 Hz, and the time was constant at 0.3 seconds. Thus the filter settings were such that waves with frequencies between 0.5 and 100 Hz could be analyzed. The EEG signals were quantified by use of fast Fourier transformation. The averaged amplitudes (square root of power) in the 11.5 to 30 Hz frequency band (F_7-C_7 lead) of each recording session were calculated and used as EEG effect measure in the kinetic-dynamic modeling procedure.

Drug analysis. Midazolam, α -hydroxymidazolam, and 2-hydroxymidazolam concentrations were analyzed by GLC according to the method of Sunzel,¹⁷ with some modifications. By use of a plasma sample of 500 μ l, the detection limit was 1 ng/ml for all three compounds and the within- and between-day coefficients of variation were less than 10%.

Protein binding. The extent of plasma protein binding of midazolam and α -hydroxymidazolam was determined for each subject by ultrafiltration at 37 $^\circ$ C by use of the Amicon Micropartition System (Amicon Div., Danvers, Mass.). Plasma samples collected before drug administration on each treatment day were pooled for each subject. Plasma aliquots of 1 ml were spiked with midazolam and α -hydroxymidazolam to obtain a concentration of 2 mg/L for both drugs. Separation of free drug from protein-bound drug was accomplished by filtration of 750 μ l plasma through an YMT ultrafiltration membrane (Amicon) at 1090g for 20 minutes at 37 $^\circ$ C, yielding about 250 μ l ultrafiltrate. Because the protein binding of several benzodiazepines has been reported to be independent of concentration over a wide concentration range (0.01 to 10 mg/L),¹⁸ plasma protein binding was determined at only one concentration.

Data analysis. The disposition of midazolam and α -hydroxymidazolam after intravenous and oral ad-

ministration to each subject were described by polyexponential equations. Different exponential models were investigated and the most suitable model was chosen according to the Akaike information criterion.^{19,20}

Basic pharmacokinetic parameters—area under the curve, clearance (CL, CL/F) volume of distribution at steady-state, terminal half-life ($t_{1/2}$), bioavailability, time of maximal drug concentration, maximal drug concentration after oral administration, and lag time—were calculated from the coefficients and exponents of the fitted functions according to standard procedures.²¹ The equilibration delay between plasma concentrations and pharmacologic effect was modeled by use of the effect compartment approach.²² The estimated steady-state plasma concentration versus effect curves after intravenous administration of midazolam and α -hydroxymidazolam were quantified by the sigmoid maximum effect (E_{max}) model.²³

The pharmacodynamic parameters of midazolam and α -hydroxymidazolam derived after intravenous administration of these compounds were used to predict the effects on EEG and peak saccadic velocity after oral administration of midazolam. To make the predictions, a simple model assuming an additive and competitive interaction was used. If two interacting compounds differ only in their potency (median effective concentration; EC_{50}) but produce the same E_{max} and have a similarly shaped (N) concentration-effect relationship, the contribution of compound 2 to the activity of compound 1 can be calculated from the following equation:

$$C_1^* = C_1 + \frac{EC_{50,1}}{EC_{50,2}} C_2 \quad (1)$$

in which C_1^* reflects the apparent "active" concentration of compound 1 in the presence of compound 2, which can be substituted in the equation of the sigmoid E_{max} model. For each subject the area inscribed by the baseline and the time versus predicted effect curve was compared with the area inscribed by baseline and the time versus observed effect curve. The areas were calculated by numeric integration of the functions from 0 to 300 minutes. Within 300 minutes the effects had returned to baseline value for each subject.

The equations were fitted to the data by use of the nonlinear regression program SIPHAR (Simed SA, Creteil, France). Statistical analysis of the effect data was performed by repeated measures ANOVA with time and treatment as factors within subjects. When significant treatment effects or treatment versus time interactions were found, the difference between treat-

Table I. Pharmacokinetic parameters of midazolam and α -hydroxymidazolam determined after intravenous administration of both compounds

	Subject No.								Mean \pm SE
	1	2	3	4	5	6	7	8	
Midazolam									
Dose (mg)	5.3	7.6	6.1	5.1	5.2	5.6	3.3	4.8	5.4 \pm 0.4
Dose (mg/kg)	0.083	0.100	0.100	0.070	0.079	0.077	0.041	0.073	0.078 \pm 0.007
CL (ml/min)	601	539	593	477	499	611	521	342	523 \pm 31
V_{ss} (L)	94	70	71	40	43	46	68	51	60 \pm 7
Terminal $t_{1/2}$ (min)	117	105	165	66	64	61	92	114	98 \pm 12
AUC ratio*	5.7	10.8	4.9	6.6	6.6	10.8	8.9	9.0	7.9 \pm 0.8
f_u (%)	2.09	2.59	2.31	2.21	2.03	2.48	3.03	2.08	2.35 \pm 0.12
α-Hydroxymidazolam									
Dose (mg)	9.6	11.4	6.9	7.5	9.9	7.8	5.0	6.5	8.1 \pm 0.7†
Dose (mg/kg)	0.150	0.150	0.113	0.103	0.150	0.108	0.063	0.098	0.117 \pm 0.011†
CL (ml/min)	660	731	662	704	682	708	728	563	680 \pm 19†
V_{ss} (L)	49	64	51	52	39	63	72	45	54 \pm 4
Terminal $t_{1/2}$ (min)	64	75	85	58	61	69	79	62	69 \pm 3†
f_u (%)	8.53	11.7	10.5	10.1	8.70	12.3	13.1	9.70	10.6 \pm 0.6†

CL, Clearance; V_{ss} , volume of distribution at steady-state; $t_{1/2}$, half-life; AUC, area under the curve; f_u , fraction unbound in plasma.

*Ratio of the AUC values of midazolam and α -hydroxymidazolam observed after intravenous administration of midazolam.

†Significantly different from corresponding value for midazolam ($p < 0.05$).

ment and placebo was tested with a paired Student *t* test at each time point (SPSS/PC+ software package, version 2.0, SPSS Inc., Chicago, Ill.). Statistical comparisons between derived pharmacokinetic and pharmacodynamic parameters were made by use of a paired Student *t* test. Significance was assumed when $p < 0.05$.

RESULTS

Clinical effects. The intravenous administration of midazolam and α -hydroxymidazolam had to be stopped before the 15-minute infusion was completed in six and five subjects, respectively, because they were unable to perform the saccadic eye movement test. All subjects were highly sedated at the end of the intravenous administrations and had difficulties performing the eye movement tests. The dose of α -hydroxymidazolam that could be administered was significantly larger than that of midazolam (Table I). The mean (\pm SE) peak concentration of midazolam was 147 ± 18 ng/ml, compared with 238 ± 49 ng/ml for α -hydroxymidazolam.

Pharmacokinetics. Figs. 1, 2, and 3 show the averaged time profiles of midazolam and α -hydroxymidazolam concentrations after the three nonplacebo treatments. The concentration-time profiles of intravenous midazolam and α -hydroxymidazolam were best described by a two-exponential equation for all subjects (Figs. 1 and 2). The individual pharmacokinetic parameters are listed in Table I. Significant differences

between the pharmacokinetic parameters of the two administered compounds were observed. The CL of α -hydroxymidazolam was significantly larger than the CL of midazolam, whereas the terminal $t_{1/2}$ was significantly shorter.

After intravenous administration of midazolam low concentrations of α -hydroxymidazolam were observed in all subjects. α -Hydroxymidazolam concentrations were on average eightfold lower (Table I) than the concentrations of midazolam. No detectable concentrations (<1 ng/ml) of the 4-hydroxymetabolite were observed. The pharmacokinetic parameters determined after oral administration of midazolam are listed in Table II. α -Hydroxymidazolam concentrations were on average 2.3-fold lower than the concentrations of midazolam, which is also reflected in the ratio of C_{max} . The 4-hydroxymetabolite was only observed in detectable amounts (>1 ng/ml) in three subjects but never exceeded concentrations of 3 ng/ml.

Pharmacodynamics. Figs. 1, 2, and 3 also show the averaged time profiles of drug effect on the EEG parameter (amplitudes in the 11.5 to 30 Hz frequency band) and peak saccadic velocity after the three nonplacebo treatments. The effects observed after placebo administration are shown in each figure for comparison. After intravenous administration of midazolam the EEG effects were significantly different from placebo ($p < 0.05$) from the first time point of effect measurement until 75 minutes after drug administration (Fig. 1, b), whereas peak saccadic velocity was

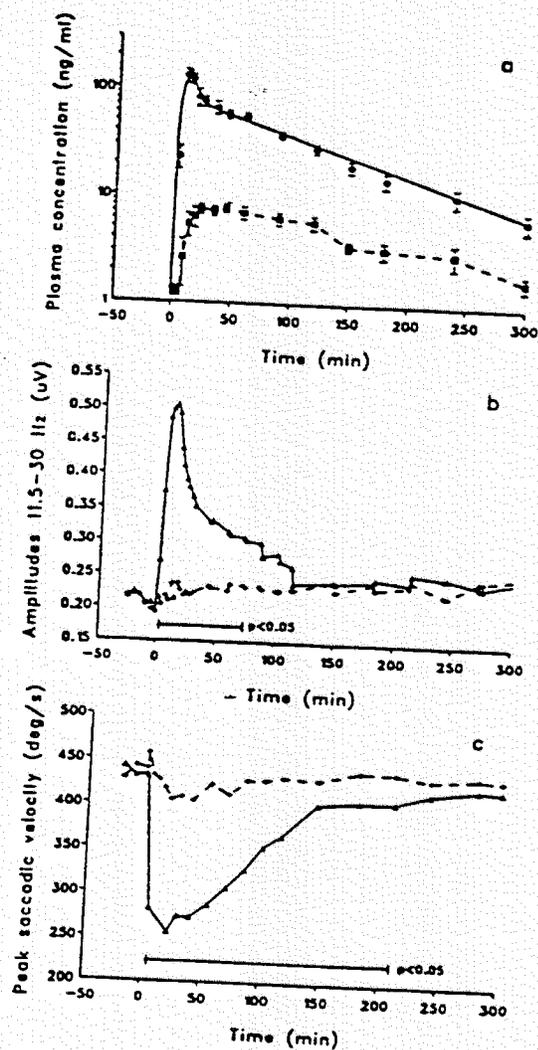


Fig. 1. a. Time profiles of midazolam (●) and α -hydroxymidazolam (■) plasma concentrations (mean \pm SE) after intravenous administration of midazolam. A biexponential equation was fitted to the pharmacokinetic data of midazolam. b. Shows the averaged time versus effect profiles of the electroencephalographic (EEG) effect measure after intravenous administration of midazolam (Δ) or placebo (+). c. Shows the averaged time versus effect profiles of the peak saccadic velocity after intravenous administration of midazolam (Δ) or placebo (+).

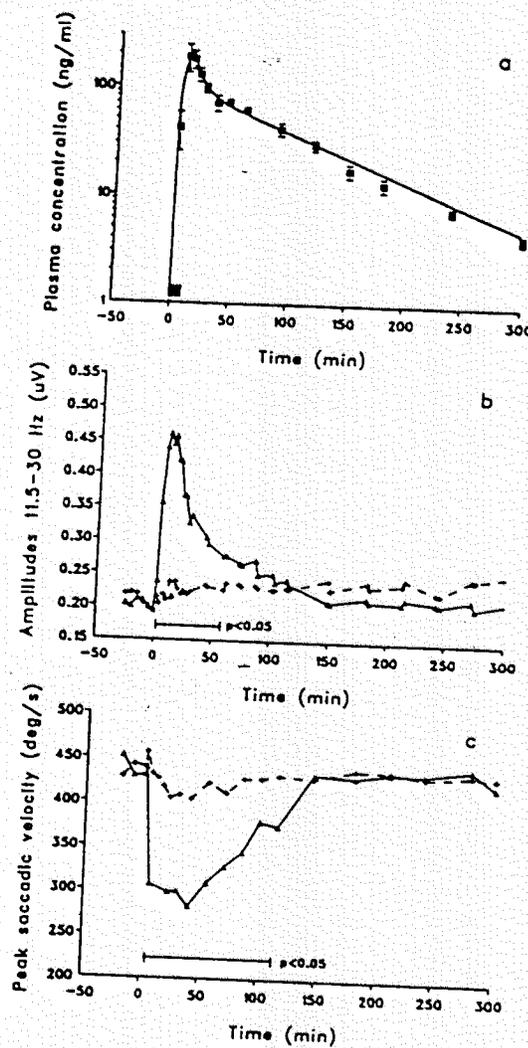


Fig. 2. a. Time profile of α -hydroxymidazolam (\blacksquare) plasma concentrations (mean \pm SE) after intravenous administration of α -hydroxymidazolam. A biexponential equation was fitted to the pharmacokinetic data of α -hydroxymidazolam. b. Shows the averaged time versus effect profiles of the EEG effect measure after intravenous administration of α -hydroxymidazolam (\blacktriangle) or placebo (+). c. Shows the averaged time versus effect profiles of the peak saccadic velocity after intravenous administration of α -hydroxymidazolam (\blacktriangle) or placebo (+).

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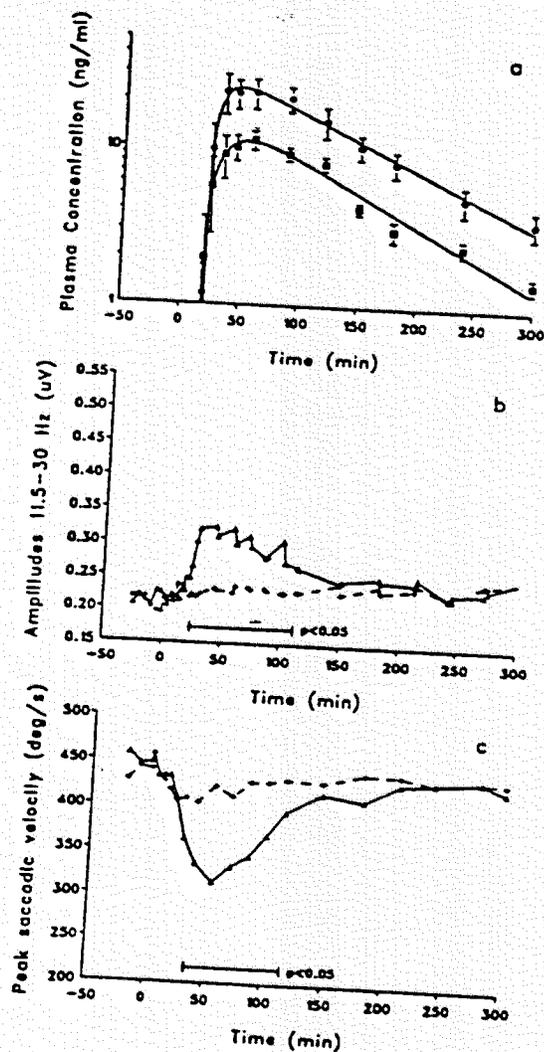


Fig. 3. a. Time profiles of midazolam (●) and α -hydroxymidazolam (■) plasma concentrations (mean \pm SE) after oral administration of midazolam. A biexponential equation was fitted to the pharmacokinetic data of midazolam and α -hydroxymidazolam b. Shows the averaged time versus effect profiles of the EEG effect measure after oral administration of midazolam (Δ) or placebo (+). c. Shows the averaged time versus effect profiles of the peak saccadic velocity after oral administration of midazolam (Δ) or placebo (+).

Table II. Pharmacokinetic parameters of midazolam and α -hydroxymidazolam determined after oral administration of 7.5 mg midazolam

	Subject No.								Mean \pm SE
	1	2	3	4	5	6	7	8	
Midazolam									
CL/F (ml/min)	4293	1276	2695	2271	3327	5555	1532	1140	2761 \pm 552
$t_{1/2}$ (min)	3.5	19	19	31	37	23	20	29	23 \pm 4
t_{max} (min)	25	36	35	64	53	45	47	49	44 \pm 4
C_{max} (ng/ml)	6.3	43	29	28	18	6.0	28	45	25 \pm 5
F (%)	14	42	22	21	15	11	34	30	24 \pm 4
α -Hydroxymidazolam									
$t_{1/2}$ (min)	25	23	19	33	39	43	24	15	28 \pm 3
t_{max} (min)	45	43	31	64	57	62	50	36	48 \pm 4
C_{max} (ng/ml)	3.6	12	22	12	7.9	4.3	11	19	12 \pm 2*
AUC ratio†	2.4	3.7	1.4	2.7	1.5	1.2	3.0	2.7	2.3 \pm 0.3

CL/F, Log mean; C_{max} , maximal concentration; $t_{1/2}$, time of C_{max} ; F, bioavailability; AUC, area under the curve.

*Significantly different from corresponding value for midazolam ($p < 0.05$).

†Ratio of the AUC values of midazolam and α -hydroxymidazolam observed after oral administration of midazolam.

decreased significantly until 210 minutes after drug administration (Fig. 1, c). The EEG effect was significantly higher than placebo until 60 minutes after administration of α -hydroxymidazolam (Fig. 2, b), whereas peak saccadic velocity was decreased significantly until 120 minutes after drug administration (Fig. 2, c). After oral administration of midazolam, EEG effects were found to be significantly higher than placebo from 30 until 105 minutes after drug intake (Fig. 3, b), whereas peak saccadic velocity was significantly decreased from 40 minutes until 115 minutes (Fig. 3, c). The relationship between plasma concentrations and effect on the EEG parameter and peak saccadic velocity were derived for each individual subject after intravenous administration of midazolam and α -hydroxymidazolam. The concentration-effect relationships were best described by the sigmoid E_{max} model for both drugs and both effect measures (Figs. 4 and 5). The pharmacodynamic parameters derived for both compounds in the individual subjects are listed in Tables III and IV by use of the EEG effect measure and peak saccadic velocity, respectively. For most of the subjects an effect compartment had to be included to account for the equilibration delay (hysteresis) between plasma concentrations and observed effect. For other subjects however, no hysteresis was observed. The concentration-EEG effect relationship of both midazolam and α -hydroxymidazolam could not be characterized for subject 3 because of the occurrence of proteresis. On the basis of both the EEG and peak saccadic velocity measurements no statistically significant differences between the pharmaco-

dynamic parameters of midazolam and α -hydroxymidazolam were observed, although the EC_{50} of α -hydroxymidazolam tended to be higher than the EC_{50} value of midazolam with use of total plasma concentrations. The mean EC_{50} values of midazolam and α -hydroxymidazolam based on free drug concentrations were 1.82 ± 0.41 and 10.2 ± 2.0 ng/ml, respectively, for the EEG effect measure. For peak saccadic velocity the values were 0.94 ± 0.18 and 5.3 ± 1.1 ng/ml, respectively. The difference in EC_{50} of midazolam and α -hydroxymidazolam based on free drug concentrations was statistically significant.

The EC_{50} values of midazolam and α -hydroxymidazolam estimated on the basis of peak saccadic velocity measurements were significantly smaller than the respective values estimated from the concentration-EEG effect relationship. A significant correlation was found ($r = 0.89$, $p < 0.05$) between the EC_{50} values derived from the two effect measures (Fig. 6).

Fig. 7 shows the averaged time profile of pharmacologic effect observed after oral administration of midazolam and the predicted time versus effect profile based on an additive and competitive interaction between midazolam and its α -hydroxymetabolite. The predicted curve represents the averaged value of the predictions for each individual. The predicted effect was calculated by use of the pharmacodynamic parameters presented in Table III and IV. Subject 3 was not included in the measured and predicted EEG effect curve. At every time point the predicted effect is considerably smaller than the actually observed effect. However, the shape of the predicted effect profile is

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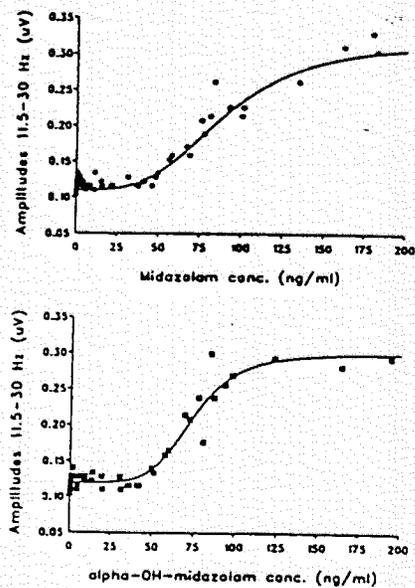


Fig. 4. Relationship between midazolam (●) and α -hydroxymidazolam (■) concentrations and EEG effect measure derived after intravenous administration of both compounds to subject 4. The solid lines represent the best fit of the sigmoid maximum effect (E_{max}) model to the actual data.

similar to the profile of the observed effects. Table V lists the predicted and observed areas between baseline and time versus effect curves of each individual. The predicted area is considerably smaller than the observed area for most of the subjects. The differences were however not statistically significant ($p = 0.055$ for EEG effect measure and $p = 0.059$ for peak saccadic velocity).

DISCUSSION

The relationship between plasma concentrations and central nervous system effects of midazolam and its main metabolite α -hydroxymidazolam were characterized after intravenous administration of both compounds to healthy volunteers. The central nervous system effects of the compounds were quantified by EEG analysis and saccadic eye movement measurements. The benzodiazepine-induced changes in the ampli-

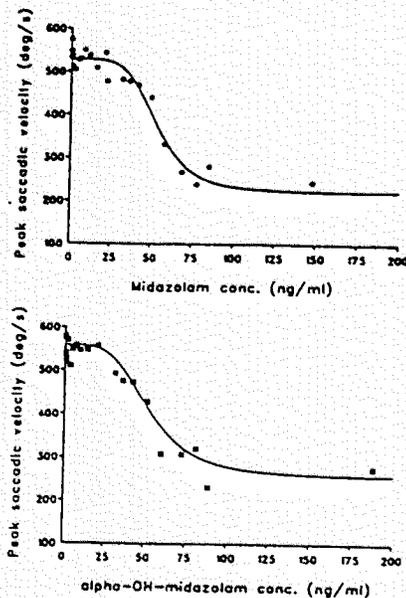


Fig. 5. Relationship between midazolam (●) and α -hydroxymidazolam (■) concentrations and peak saccadic velocity derived after intravenous administration of both compounds to subject 4. The solid lines represent the best fit of the sigmoid E_{max} model to the actual data.

tudes in the 11.5 to 30 Hz (beta) frequency band of the EEG signals was used as EEG effect measure. Animal studies have shown recently that the changes in activity in the 11.5 to 30 Hz (beta) frequency band closely correlated with the affinity and intrinsic efficacy of benzodiazepines at the central γ -aminobutyric acid-benzodiazepine receptor complex, thus providing evidence for the pharmacologic relevance of this effect measure.^{4,23}

Measurements of saccadic eye velocity have also been used successfully to characterize concentration-effect relationships of benzodiazepines^{16,24,25} and to study the rate of entry of these drugs into the central nervous system.²⁶ That fatigue produces changes in saccadic eye movements similar to those observed after benzodiazepine administration suggests that peak saccadic velocity may be a relevant measure of benzodiazepine induced impaired performance.^{27,28}

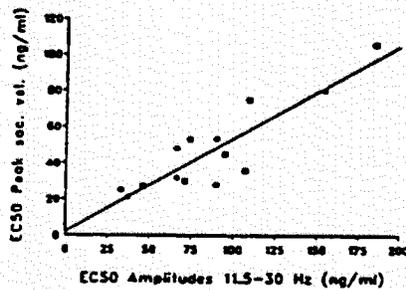


Fig. 6. Correlation ($r = 0.89$, $p < 0.05$) between the individual median effective concentration (EC_{50}) values of midazolam (\bullet) and α -hydroxymidazolam (\blacksquare) estimated by use of the amplitudes in the 11.5 to 30 Hz frequency band of the EEG signals and peak saccadic velocity as effect measures.

The intravenous administration of midazolam and α -hydroxymidazolam was maintained until the subjects were too sedated to perform the saccadic eye movement test. The larger dose of α -hydroxymidazolam that could be administered indicates the potency difference between the two compounds. However, the difference in effect is determined by differences in both the pharmacokinetic and pharmacodynamic properties of the two compounds. The pharmacokinetic parameters of midazolam were similar to the values determined in other studies.^{11,29,30} The α -hydroxymetabolite was found to be cleared 1.3 times more rapidly than the parent compound, which was also reflected in a shorter terminal $t_{1/2}$ (Table I). The rapid elimination of α -hydroxymidazolam may explain why only low concentrations of this metabolite are found after intravenous administration of the parent compound (Fig. 1 and Table I). The peak concentrations of α -hydroxymidazolam at the end of the infusion were 1.6 times higher than the peak midazolam concentrations. This difference in peak concentration is almost similar to the difference in dose. The peak concentration of midazolam (148 ng/ml) was close to the range of 150 to 200 ng/ml in which patients could be aroused and responded verbally after sedation with midazolam.³¹

The concentration-effect relationships of midazolam and α -hydroxymidazolam were characterized by the sigmoid E_{max} model in virtually all individual subjects and for both effect measurements (Figs. 4 and 5). No statistically significant differences between the pharmacodynamic parameters of midazolam and

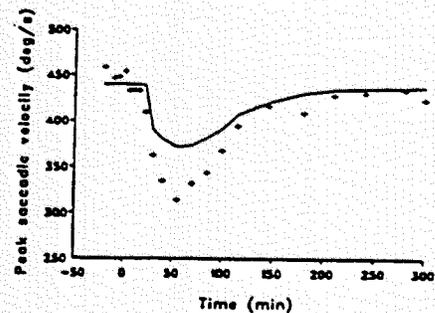
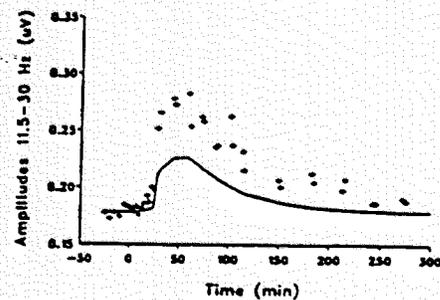


Fig. 7. Averaged time versus effect profiles of the EEG effect measure and peak saccadic velocity, respectively, after oral administration of midazolam (\bullet). The solid lines represent the predicted effect, assuming an additive and competitive interaction between midazolam and α -hydroxymidazolam.

α -hydroxymidazolam were observed for both effect measures, although the EC_{50} of midazolam tended to be smaller than the value estimated for the metabolite. These findings show that the α -hydroxymetabolite is at least as potent as its parent compound and may contribute significantly to the effects of the parent drug when present in sufficiently high concentrations.

Apart from an estimation of the pharmacodynamics of the metabolite, its interaction with the parent compound should also be characterized to predict the impact of the metabolite on the effects of the parent compound in practice. Oral administration of midazolam reflects such a practical situation in which relatively high metabolite concentrations are observed as a result of a substantial first-pass metabolism of midazolam (Fig. 3, a, and Table II). The observed bioavail-

Table III. Pharmacodynamic parameters of midazolam and α -hydroxymidazolam determined from the EEG measurements

	Subject No.								Mean \pm SE
	1	2	4	5	6	7	8		
Midazolam									
k_{eq} (min^{-1})	1.08	—*	1.23	—*	0.49	—*	0.27	0.77 \pm 0.23	
E_0 (μV)	0.27	0.15	0.11	0.16	0.20	0.18	0.24	0.19 \pm 0.02	
E_{max} (μV)	0.34	0.32	0.21	0.24	0.21	0.39	0.37	0.30 \pm 0.03	
EC_{50} (ng/ml)	33	154	90	66	90	37	66	77 \pm 15	
N	2.7	3.4	3.4	2.9	2.2	4.3	2.6	3.1 \pm 0.3	
α-Hydroxymidazolam									
k_{eq} (min^{-1})	0.41	0.63	0.91	0.42	0.61	0.4	—*	0.56 \pm 0.08	
E_0 (μV)	0.25	0.16	0.12	0.12	0.17	0.15	0.17	0.16 \pm 0.02	
E_{max} (μV)	0.52	0.25	0.18	0.30	0.26	0.24	0.27	0.29 \pm 0.04	
EC_{50} (ng/ml)	107	185	74	109	95	46	71	98 \pm 17	
N	2.0	3.4	5.4	2.2	2.3	4.2	2.4	3.1 \pm 0.5	

k_{eq} : First-order rate constant of equilibration between plasma and effect site; E_0 : baseline effect; E_{max} : maximal effect; EC_{50} : steady-state plasma concentration producing 50% of E_{max} ; N: steepness of concentration-effect relationship.

*No hysteresis detectable.

Table IV. Pharmacodynamic parameters of midazolam and α -hydroxymidazolam determined from the saccadic eye measurements

	Subject No.								Mean \pm SE
	1	2	3	4	5	6	7	8	
Midazolam									
k_{eq} (min^{-1})	0.16	0.08	0.16	—*	0.32	0.13	—*	0.07	0.15 \pm 0.04
E_0 (deg/sec)	388	501	530	529	391	376	335	310	432 \pm 28
E_{max} (deg/sec)	-145	-275	-329	-306	-198	-139	-128	-59	-197 \pm 34
EC_{50} (ng/ml)	25	80	33	53	48	28	21	32	40 \pm 7
N	5.5	0.9	0.9	5.2	4.3	3.3	12.0	3.6	4.5 \pm 1.2
α-Hydroxymidazolam									
k_{eq} (min^{-1})	0.051	0.067	0.23	0.16	0.047	0.13	0.14	0.37	0.15 \pm 0.04
E_0 (deg/sec)	415	515	511	559	379	390	426	319	439 \pm 29
E_{max} (deg/sec)	-101	-282	-211	-301	-121	-148	-128	-73	-171 \pm 30
EC_{50} (ng/ml)	36	106	26	53	75	45	27	30	49 \pm 10
N	5.4	1.4	4.9	4.0	2.7	3.1	11.1	5.0	4.7 \pm 1.0

k_{eq} : First-order rate constant of equilibration between plasma and effect site; E_0 : baseline effect; E_{max} : maximal effect; EC_{50} : steady-state plasma concentration producing 50% of E_{max} ; N: steepness of concentration-effect relationship.

*No hysteresis detectable.

ability after oral administration of 7.5 mg midazolam was only 24%, which is considerably less than the values reported in other studies.^{11,32} However, in those studies higher doses of midazolam were administered, and it has been suggested that the bioavailability of midazolam increases with higher oral doses as a result of saturation of first-pass metabolism.¹³ After intravenous administration of midazolam the α -hydroxymidazolam concentrations were on average eightfold lower than midazolam concentrations. However, after oral administration this ratio was decreased to 2.3, which was also reflected in the ratio of peak

plasma concentrations of both compounds. By assumption of an additive and competitive interaction between midazolam and its α -hydroxymetabolite and after the EC_{50} of both compounds was taken into account, these concentration ratios indicate that α -hydroxymidazolam would only contribute to an extent of about 10% to the observed effects after intravenous administration of midazolam and about 34% after oral administration of midazolam.

The changes in EEG effect and peak saccadic velocity after oral administration closely follow the plasma concentration-time profiles of midazolam and

Table V. Comparison of predicted and observed area between the baseline and the time versus effect curve after oral administration of midazolam

Subject No.	Amplitudes of 11.5 to 30 Hz:		Peak saccadic velocity	
	Predicted (min · μ V) ^a	Observed (min · μ V) ^b	Predicted (10° degrees)	Observed (10° degrees)
1	2.11	26.3	0.26	79.4
2	0.38	4.77	88.2	97.7
3	—	—	97.4	119
4	0.31	2.64	17.5	108
5	1.05	6.76	2.78	40.0
6	0.16	4.79	1.52	55.4
7	10.7	11.4	80.6	49.6
8	12.1	19.3	42.9	41.8
Mean ± SE	3.83 ± 1.97	10.9 ± 3.34	41.4 ± 14.8	73.9 ± 11.1

^aArea calculated on the basis of the Hill equation, equation 1, the pharmacodynamic parameter estimates in Table II, and the observed concentrations of midazolam and α -hydroxymidazolam.

^bMeasured area of the time versus effect curve.

α -hydroxymidazolam. The distinct lag time observed in the pharmacokinetic profile after oral administration is also apparent from the effect versus time profile and the plasma concentrations and effects appear to peak at approximately the same time (Fig. 3). Unfortunately, in virtually all of the subjects the observed effects were too small to allow a quantification of the interaction between midazolam and its α -hydroxymetabolite by an appropriate pharmacodynamic interaction model. As an alternative, the predicted pharmacologic effects, assuming an additive and competitive interaction between midazolam and its α -hydroxymetabolite, were compared with the actual observed effects (Fig. 7 and Table V). The assumptions underlying the interaction model are probably valid because both compounds have similarly shaped concentration-effect relationships and produce the same maximal effect. Fig. 7 shows that, on average, the observed effects after oral administration of midazolam cannot be predicted by a simple additive and competitive interaction between midazolam and its α -hydroxymetabolite. However, the mean difference in predicted and observed area under the time versus effect curves were not statistically significant (Table V). For two subjects (Nos. 7 and 8) a reasonable agreement between the time profiles of predicted and observed effects was found. The fact that for most subjects the actual observed effects were considerably larger at each time point than the predicted effects suggested that a synergistic interaction between both compounds may have occurred. However, a synergistic interaction is unlikely considering the same mechanism of action of midazolam and α -hydroxymidazolam. Other factors, such as fatigue, formation of other metabolites, or an

interaction at the level of plasma protein binding, may also have contributed to the discrepancy between predicted and observed effects after oral administration. However, the other known active metabolite of midazolam, 4-hydroxymidazolam, was observed in only very low concentrations that did not exceed 3 ng/ml in any one of the subjects. Thus it seems unlikely that this metabolite contributed to the effects. In addition, a competitive interaction between midazolam and α -hydroxymidazolam at the level of plasma protein binding is also an unlikely explanation because the degree of plasma protein binding of benzodiazepines (including midazolam) has been shown to be linear over a wide concentration range.¹⁸ The reason why the simple interaction model cannot predict the effects accurately remains unclear and requires further investigation.

For a comparison of the absolute potency difference of midazolam and α -hydroxymidazolam, the EC_{50} referenced to unbound drug should be used.⁴ A fivefold potency difference based on unbound drug EC_{50} was observed because α -hydroxymidazolam is significantly less protein bound than midazolam (Table I). This fivefold potency difference based on free drug EC_{50} corresponds with the difference in receptor affinity of both compounds.²³ This shows that, apart from receptor affinity, protein binding has to be taken into consideration for prediction of the effects of the metabolite on basis of *in vitro* data.

On the basis of EC_{50} values, peak saccadic velocity measurements are approximately two times more sensitive to benzodiazepine effects than amplitudes in the beta frequency band of the EEG signals (Tables III and IV and Fig. 6). This was also apparent from the

time-effect relationships after intravenous administration of midazolam and α -hydroxymidazolam (Figs. 1 and 2). The peak saccadic velocity measurements detected the effects of midazolam and α -hydroxymidazolam for a considerably longer time period than the EEG measurements. Nevertheless, a correlation was found between the EC_{50} values estimated by the two effect measurements (Fig. 6). This indicates that peak saccadic velocity and amplitudes in the beta frequency band of the EEG signals show the same interindividual variability with respect to the effects of midazolam and α -hydroxymidazolam. The EC_{50} values of midazolam based on EEG and peak saccadic velocity measurements were smaller than the EC_{50} values derived on basis of psychomotor performance tests, such as reaction time ($EC_{50} = 104$ ng/ml) and tracing tests ($EC_{50} = 171$ ng/ml).¹⁴ Persson et al.¹¹ determined midazolam concentrations in a group of patients at various end points of recovery from midazolam sedation after anaesthesia with high doses of this drug. The EC_{50} to recall one's name and date of birth was 173 ng/ml, to recover from arousable to drowsy was 116 ng/ml, and to recover from drowsy to awake was 53 ng/ml. These findings indicate that peak saccadic velocity is a sensitive measure of benzodiazepine effect on the central nervous system.

In conclusion, the concentration-effect relationships of midazolam and its main metabolite α -hydroxymidazolam could be quantified very well in individual subjects by use of saccadic eye movement and EEG effect measurements, yielding approximately the same pharmacodynamic parameters for both compounds. The effects observed after oral administration were substantially larger than those predicted by an additive and competitive interaction between midazolam and its α -hydroxymetabolite. This lack of predictive power of the models used in this study requires further investigation. α -Hydroxymidazolam is almost as equipotent as midazolam with respect to the measured effects and contributes significantly to those effects of midazolam after oral administration.

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PHARMACOKINETICS AND DRUG DISPOSITION

Midazolam should be avoided in patients receiving the systemic antimycotics ketoconazole or itraconazole

Interaction between ketoconazole, itraconazole, and midazolam was investigated in a double-blind, randomized crossover study of three phases at intervals of 4 weeks. Nine volunteers were given either 400 mg ketoconazole, 200 mg itraconazole, or matched placebo orally once daily for 4 days. On day 4, the subjects ingested 7.5 mg midazolam. Plasma samples were collected and psychomotor performance was measured. Both ketoconazole and itraconazole increased the area under the midazolam concentration-time curve from 10 to 15 times ($p < 0.001$) and mean peak concentrations three to four times ($p < 0.001$) compared with the placebo phase. In psychomotor tests (e.g., the Digit Symbol Substitution Test), the interaction was statistically significant ($p < 0.05$) until at least 6 hours after drug administration. Inhibition of the cytochrome P450III_A by ketoconazole and itraconazole may explain the observed pharmacokinetic interaction. Prescription of midazolam for patients receiving ketoconazole and itraconazole should be avoided. (CLIN PHARMACOL THER 1994;55:481-5.)

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Erythromycin administration increases and prolongs the effects of midazolam to the extent that its hypnotic effect can no longer be regarded to be of short duration.¹ Because studies *in vitro*² suggest that the metabolism of midazolam is also inhibited by ketoconazole and itraconazole, we have studied their potential interaction with oral midazolam in healthy volunteers.

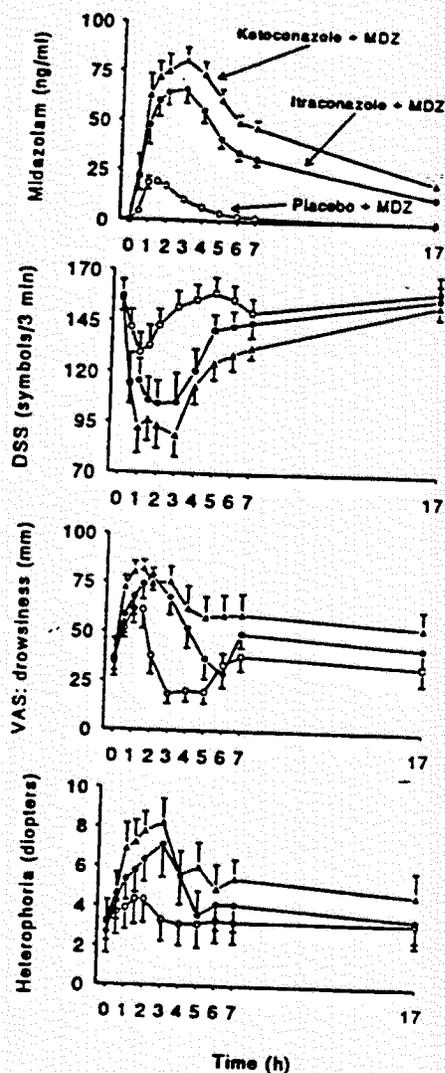


Fig. 1. Concentrations (mean \pm SEM) of midazolam (MDZ) in plasma and results of Digit Symbol Substitution Test (DSS) and Maddox wing test (heterophoria), and subjective drowsiness (visual analog scale; VAS) after an oral dose of 7.5 mg midazolam following pretreatment with oral ketoconazole (400 mg), itraconazole (200 mg), or placebo for 4 days to nine healthy volunteers. *Open circles*, concentrations and psychomotor effects of midazolam after placebo; *solid triangles*, concentrations and psychomotor effects of midazolam after ketoconazole; *solid circles*, concentrations and psychomotor effects of midazolam after itraconazole.

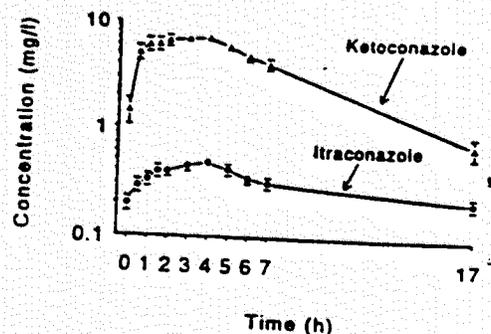


Fig. 2. Concentrations (mean \pm SEM) of ketoconazole and itraconazole in plasma during the fourth day of treatment with oral ketoconazole (400 mg) or itraconazole (200 mg) for 4 days to nine healthy volunteers. Ketoconazole and itraconazole had been taken 1 hour before the 0-hour blood sample. *Solid triangles*, Ketoconazole; *solid circles*, itraconazole.

MATERIAL AND METHODS

Study design. We obtained informed written consent and institutional approval to study two male and seven female volunteers (age range, 19 to 26 years; weight range, 52 to 85 kg). We used a randomized, double-blind crossover study design in three phases, at intervals of 4 weeks. The subjects were given either 400 mg ketoconazole (Nizoral, Orion, Helsinki, Finland), 200 mg itraconazole (Sporanox, Orion), or placebo orally at 2 PM daily for 4 days. On day 4, the subjects ingested 7.5 mg midazolam (Dormicum, Hoffmann-La Roche, Basel, Switzerland) with 150 ml water at 3 PM. The volunteers fasted for 3 hours before administration of midazolam and had a standard meal 4 hours afterward. Ingestion of alcohol, coffee, tea, and cola was not allowed during the test days, and smoking was not permitted.

Blood sampling and determination of midazolam and antimycotics. Blood was sampled into tubes containing ethylenediaminetetra-acetic acid before the study and once during the pretreatments for the control of compliance. On day 4, timed samples were drawn immediately before administration of midazolam and $\frac{1}{2}$, 1, 1½, 2, 3, 4, 5, 6, 7, and 17 hours after administration. Plasma was separated within 30 minutes and stored at -40°C until analyzed. Midazolam concentrations were analyzed with gas chromatography,³ and ketoconazole and itraconazole concentrations were analyzed by HPLC.^{4,5}

Pharmacokinetics of midazolam and antimycotics. Pharmacokinetics of midazolam and the antimycotics

Table I. Pharmacokinetic parameters of midazolam (mean \pm SEM) after administration of 7.5 mg oral midazolam following pretreatment with oral ketoconazole (400 mg), itraconazole (200 mg), or placebo for 4 days to nine healthy volunteers

Parameter	Placebo (control)	Ketoconazole	Itraconazole
C_{max} (ng \cdot ml $^{-1}$)	22 \pm 6	90 \pm 7*	75 \pm 7*
% of control	100	410	340
t_{max} (min)	80 \pm 26	147 \pm 27†	123 \pm 19
AUC(0- ∞) (μ g \cdot ml $^{-1}$ \cdot min)	3.9 \pm 0.6	62 \pm 6*	42 \pm 6‡
% of control	100	1590	1080
$t_{1/2}$ (hr)	2.8 \pm 0.6	8.7 \pm 1.0*	7.9 \pm 0.5*
% of control	100	310	280

C_{max} : Maximum plasma concentration; t_{max} : time to reach C_{max} ; AUC(0- ∞): area under the plasma concentration-time curve; $t_{1/2}$: half-life.
*Significantly ($p < 0.001$) different from placebo phase.
†Significantly ($p < 0.05$) different from placebo phase.
‡Significantly ($p < 0.005$) different from ketoconazole phase.

were characterized by area under the drug plasma concentration-time curves [AUC(0- ∞)], calculated with use of the trapezoidal rule, peak concentrations (C_{max}), and peak concentration times (t_{max}). For midazolam, we also calculated elimination half-lives ($t_{1/2}$).⁶

Psychomotor tests. The effects of midazolam on psychomotor performance were assessed at the time of blood sampling by use of a battery of tests. In the Digit Symbol Substitution Test (DSST), the number of digits correctly substituted by simple symbols in 3 minutes was recorded.⁷ The Maddox wing test was used to measure the coordination of extraocular muscles.⁸ Subjective effects were recorded on 17 horizontal visual analog scales that were 100 mm in length (e.g., alert-drowsy).⁹

Statistical analysis. All data were expressed as mean values \pm SEM. Data were analyzed with the statistical program Systat for Windows, version 5.0 (Systat, Evanston, Ill.). ANOVA with repeated measures was used; a posteriori testing was done with Tukey's test. The Pearson product-moment correlation coefficient was used to investigate the possible relationship between the ratio of the AUC(0- ∞) of midazolam during the ketoconazole and itraconazole phases to the AUC(0- ∞) of midazolam during the placebo phase and the C_{max} of ketoconazole and itraconazole. Differences were regarded statistically significant if $p < 0.05$.

RESULTS

During the ketoconazole phase, the AUC(0- ∞) of midazolam was more than 15 times higher and the C_{max} was more than four times higher than those observed during the placebo phase. Itraconazole increased the AUC(0- ∞) of midazolam by 10 times and

the C_{max} by three times (Fig. 1 and Table I). Ketoconazole and itraconazole increased the $t_{1/2}$ of midazolam from 2.8 \pm 0.6 hours to 8.7 \pm 1.0 and 7.9 \pm 0.5 hours, respectively. During the ketoconazole phase, the mean concentration of midazolam was still higher than the C_{max} of midazolam without antimycotics 17 hours after midazolam. The plasma ketoconazole and itraconazole concentrations were 1.5 \pm 0.4 and 0.20 \pm 0.03 mg/L, respectively, at the time midazolam was given (Fig. 2). There was a significant linear correlation ($r = 0.784$; $p < 0.05$) between the ratio of the AUC(0- ∞) of midazolam during the ketoconazole phase to the AUC(0- ∞) of midazolam during the placebo phase and the C_{max} of ketoconazole. On the other hand, the correlation between the corresponding AUC ratio and the C_{max} of itraconazole was statistically not significant (Fig. 3).

The higher concentrations of midazolam during treatment with antimycotics were associated with profound sedative effects (Fig. 1). ANOVA revealed a statistically significant difference between treatments in all psychomotor tests, the DSST ($p < 0.001$), the Maddox wing test ($p < 0.005$), and in subjective drowsiness ($p < 0.001$). During the ketoconazole phase all psychomotor variables differed significantly ($p < 0.05$) from the placebo phase for at least 6 hours. Differences between itraconazole and placebo phases appeared to be smaller.

DISCUSSION

In this study both ketoconazole and itraconazole markedly affected the pharmacokinetics of midazolam and increased its pharmacodynamic effects in young adults. Pretreatment with ketoconazole or itraconazole once daily for 4 days resulted in a 10- to 15-fold increase in AUC(0- ∞) values for orally administered mi-

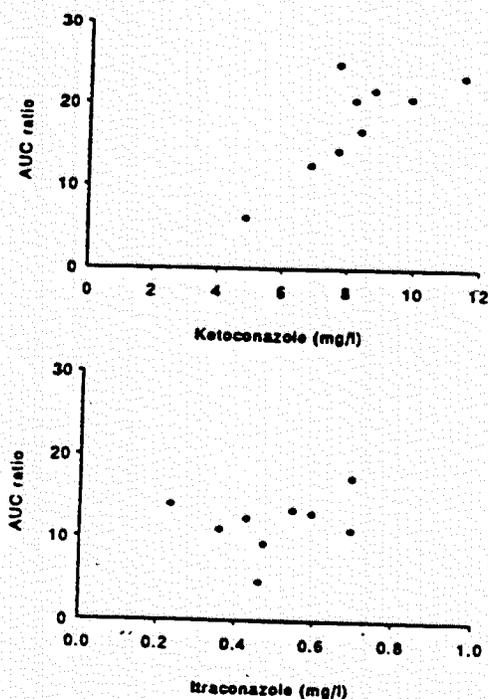


Fig. 3. Relation of the ratio of the area under the plasma concentration-time curve [$AUC(0-\infty)$] of midazolam during ketoconazole and itraconazole phases to $AUC(0-\infty)$ of midazolam during the placebo phase and the maximum concentration of ketoconazole and itraconazole. Oral dose of midazolam was 7.5 mg.

dazolam. Because midazolam undergoes significant first-pass metabolism and has an oral bioavailability less than 50%,¹⁰ this change resulted most likely from an increase in oral bioavailability and a decrease in plasma clearance of midazolam.

Administration of midazolam after ketoconazole or itraconazole also resulted in undesirably severe and excessively long-lasting hypnotic effects. Despite the small 7.5 mg dose of midazolam, the volunteers could hardly be wakened during the first hour after midazolam administration, and most experienced amnesia lasting for several hours. The scores on the DSST, for example, were still statistically significantly different between the placebo and ketoconazole and itraconazole phases 6 hours after administration of midazolam. Patients ingesting even a dose only of 7.5 mg

midazolam during ketoconazole and itraconazole treatment are not likely to be capable of tasks that require skills (e.g., driving a car) 6 hours after midazolam administration, as suggested by the manufacturer.

Compared with our previous study on the forceful interaction between erythromycin and midazolam,¹ the interaction between ketoconazole or itraconazole and midazolam is even stronger. Erythromycin increased the area under the midazolam concentration-time curve approximately four times because of the decrease in plasma clearance and increase in oral bioavailability. Based on the change of the $AUC(0-\infty)$ of midazolam, the interaction between ketoconazole and midazolam is even 400% stronger than the interaction between erythromycin and midazolam. Unlike erythromycin, which decreased the t_{max} of midazolam in our previous study, the azole antimycotics appeared to prolong the t_{max} of midazolam in a minor degree or to leave it unchanged. This is not surprising because erythromycin, as a motilin-agonistic agent, has been shown to improve gastric emptying.¹¹

Midazolam is metabolized by cytochrome P450III_A isozyme,¹² and studies in vitro have suggested that an interaction between midazolam and ketoconazole and itraconazole is probable.² The present study confirms the results obtained in vitro and is in good agreement with previous reports on the interactions of ketoconazole and itraconazole with drugs metabolized by cytochrome P450III_A isozyme (e.g., cyclosporine).^{13,14} The interaction between ketoconazole and itraconazole and orally administered midazolam is clearly of major clinical significance. Because triazolam, another short-acting hypnotic in wide clinical use, is metabolized mainly by the same P450III_A isozyme,¹² our concern can probably also be extended to triazolam. The clinical implication of this study is that clinicians should know that these antimycotics may dangerously increase the deepness of sleep and prolong the hypnotic effect of orally administered midazolam. Prescription of midazolam for patients receiving ketoconazole and itraconazole should be avoided or the dose should be greatly reduced. Patients using these antimycotics should be informed of the possibility of the enhanced and prolonged hypnotic effect of midazolam.

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Pharmacokinetics of Midazolam Following Intravenous and Oral Administration in Patients with Chronic Liver Disease and in Healthy Subjects

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To study the effects of cirrhosis of the liver on the pharmacokinetics of midazolam single IV (7.5 mg as base) and p.o. (15.0 mg as base) doses of midazolam were administered to seven patients with cirrhosis of the liver and to seven healthy control subjects. One cirrhotic patient did not receive the oral dose. The distribution of midazolam in both study groups was alike as indicated by similar values of $t_{1/2\alpha}$, V_1 and V_d . Also the plasma protein binding of midazolam was unchanged in the patients with cirrhosis. The elimination of midazolam was significantly retarded in the patients as indicated by its lower total clearance (3.34 vs. 5.63 ml/min/kg), lower total elimination rate constant (0.400 vs. 0.721 h^{-1}), and longer elimination half-life (7.36 vs 3.80 h). The bioavailability of oral midazolam was significantly ($P < 0.05$) higher in patients than controls (76% vs. 38%). The antipyrine-half-life was 32.4 h in the patients and 11.8 h in the controls. There were statistically significant ($P < 0.01$) correlations between the clearances of the two drugs ($r = 0.680$) and between their half-lives ($r = 0.755$). The hypnotic effects of midazolam were similar in both groups. However, on a pharmacokinetic basis a reduced dosage of midazolam to patients with advanced cirrhosis of the liver is recommended.

Midazolam is a new benzodiazepine derivative which differs from the other members of this group in view of its pharmacokinetics and duration of action. The elimination half-life of midazolam is short, only 1.3–2.5 h. It is eliminated through metabolism, less than 1% of IV dose being recovered intact in the urine. Midazolam metabolites are hydroxylated derivatives, α -hydroxy-midazolam, 4-hydroxy-midazolam and α -4-dihydroxy-midazolam.¹ The α -hydroxy-midazolam has been shown to have some pharmacological activity in man.² About 30% of oral dose undergoes first-pass metabolism in the liver.³ This first-pass metabolism and rapid elimination are typical of midazolam and separate it from other benzodiazepines.⁴ On the other hand, it is quite proba-

ble—in view of these properties—that midazolam kinetics will be altered in conditions where liver function is impaired. Cirrhosis of the liver could be expected to decrease midazolam first-pass metabolism, thus increasing its systemic availability and also delaying its elimination. However, this aspect has not been examined in depth. The present study was conducted to investigate the effect of cirrhosis of the liver on the pharmacokinetics of midazolam.

PATIENTS AND METHODS

Patients and Healthy Volunteers

The pharmacokinetic study with intravenous and oral midazolam was performed in a group of patients with chronic liver disease and in a sex and age matched control group of healthy volunteers.

Seven men with chronic liver disease took part. Their clinical characteristics are listed in Table 1. The diagnosis of liver disease was verified histologically in six patients. In one patient (patient number

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TABLE I

Clinical Characteristics of the Patients with Cirrhosis of the Liver and Healthy Volunteers* Who Participated in the Pharmacokinetic Study with Midazolam

Pat. No.	Age (yr)	Weight (kg)	S-ASAT ^a (U/l)	S-Alp ^a (U/l)	S-Bil ^a (umol/l)	P-TT ^a	S-Alb ^a (g/l)	S-Crea (ml/min)	Antipyr ^a (ml/min/kg)	Antipyr ^a (h)	Ascite	Oedem	Smoker	Medication
1	67	74	427	825	235	0.51	18.7	86	0.17	38.5	+	-	No	Spironolactone
2	38	108	96	407	121	0.44	28.3	81	0.13	51.3	-	-	Yes	Furosemide
3	37	89	90	1161	248	1.10	36.8	58	0.33	19.6	+	-	Yes	—
4	60	87	1390	1681	169	0.72	27.3	120	0.32	24.0	+	+	Yes	Spironolactone
5	30	71	61	271	64	0.62	28.2	79	0.19	37.7	-	-	Yes	Spironolactone
6	46	81	54	240	87	0.61	32.7	45	0.24	33.2	-	+	Yes	—
7	58	86	20	160	154	1.12	37.4	64	0.33	22.8	-	-	No	Amiloride, Hydrochlorothiazide, Metoprolol, Glibenclamide
Mean	48.0	85.1	305	665	154	0.73	29.9	76	0.244 ^a	32.4 ^a				
± SD	13.9	12.2	497	553	77	0.27	6.5	24	0.08	10.3				
Healthy volunteers (N = 7)														
Mean	44.3	79.4	29	139	5.6	1.02	35.2	76	0.719	11.8	-	-	5 Yes	None
± SD	9.5	15.1	18	27	2.6	0.21	3.3	13	0.248	3.5			2 No	

* all males; ^aserum alanine aminotransferase; ^aserum alkaline phosphatase; ^aserum bilirubin; ^aplasma thromboplastin activity (Thrombotest); ^aserum albumin.

min; ^aserum creatinine; ^aantipyrine clearance; ^aantipyrine half-life; -: lacking; +: present; ^asignificantly different from control, P < 0.001.

6) the diagnosis was based on long history of alcohol abuse, typical clinical findings of cirrhosis of the liver with elevated portal pressure, and results of liver function tests suggesting advanced impairment of liver function.

The control group consisted of seven healthy male volunteers (Table 1). They were considered healthy on the basis of history, physical examination, and the results of routine tests for renal, hepatic, and haematopoietic functions. The patients and control subjects were asked not to drink alcoholic beverages for at least one week before the study.

The protocol of the study was accepted by the local ethics committee. Informed consent was obtained from the patients and volunteers before starting the study.

Study Procedures

An intravenous dose of midazolam HCl of 8.35 mg (7.5 mg as base) was given as a bolus injection to all patients and control subjects. On a separate occasion, at least three days later an oral dose of 20.3 mg of midazolam maleate (15 mg as base) (Dormicum[®], Roche) was given to the same control subjects and patients, except for one patient (patient number 1) with cirrhosis of the liver. The oral dose was given with about 200 ml of fruit juice. The doses were given in a randomized order and the studies were

started in the morning after an overnight fast. The fasting was continued up to 4 h after the dose, during which time the patients and healthy volunteers remained recumbent.

Sampling

Samples of venous blood (10 ml) were drawn through an indwelling polyethylene cannula in a forearm vein into heparinized tubes according to the following time schedule: 0, 5, 15, 30, 45 min and 1, 2, 4, 6, 8, 12, 16, and 24 hours after the dose. The plasma was separated by centrifugation and stored frozen (-20°C) until analyzed.

Antipyrine Test

To determine the capacity of the liver to metabolize drugs an antipyrine test was performed on all subjects. The dose of antipyrine was 10 mg/kg orally and it was given concurrently with the intravenous administration of midazolam. Blood samples for antipyrine assay were taken at 3, 6, 9, 12, and 24 hours in the healthy controls. In the patients additional samples were obtained for up to 72 hours after the antipyrine dose. The antipyrine concentration in the plasma was measured by HPLC.⁵ Antipyrine clearance and half-life were calculated as previously described.⁶

Analysis of Midazolam

Concentrations of unchanged midazolam in plasma samples were determined by electron capture gas liquid chromatography.⁷ The method separates midazolam from its main metabolite, α -hydroxy-midazolam. The sensitivity of the method was 2 $\mu\text{g/L}$ and the coefficient of variation was less than 5% at a concentration level of 50 $\mu\text{g/L}$.

Protein Binding of Midazolam

The plasma protein binding of midazolam was determined by equilibrium dialysis after the addition of a tracer dose of (C^{14})-midazolam to plasma samples; 1.0 ml of plasma was dialysed at 30°C. for 24 h. against phosphate buffer pH 7.4 (8).

Pharmacokinetic Analysis

Plasma concentration-time curves were fitted to a biexponential equation (midazolam IV and antipyrine p.o.) or triexponential equation (midazolam p.o.) using the nonlinear least squares computer program NONLIN⁹ in its translation to BASIC.¹⁰ The weighting factors were reciprocals of the squared plasma concentrations.²

Routine methods were used to calculate the clearance and distribution of midazolam after intravenous administration.¹¹ The total clearance of midazolam was calculated from the equation

$$CL = \frac{\text{Dose}}{\text{AUC}}$$

where AUC is the area under serum concentration-time curve calculated by the trapezoidal rule up to the last measured midazolam concentration value and corrected for infinity. The different volumes of distribution were calculated from the equations

$$V_1 = \frac{\text{Dose}}{A + B}$$

$$V_{ss} = \frac{k_{12} + k_{21}}{k_{21}} \cdot V_1$$

where V_1 = volume of central compartment, V_{ss} = volume at steady state, and k_{12} and k_{21} are the rate constants between the central and peripheral compartments.

Bioavailability (F) of the oral doses was determined with reference to the intravenous dose by comparing of the respective areas and the concentration-time curves after correction for β -values according to the equation

$$F = \frac{\text{AUC p.o.} \cdot \text{Dose IV} \cdot \beta_{\text{p.o.}}}{\text{AUC IV} \cdot \text{Dose p.o.} \cdot \beta_{\text{IV}}}$$

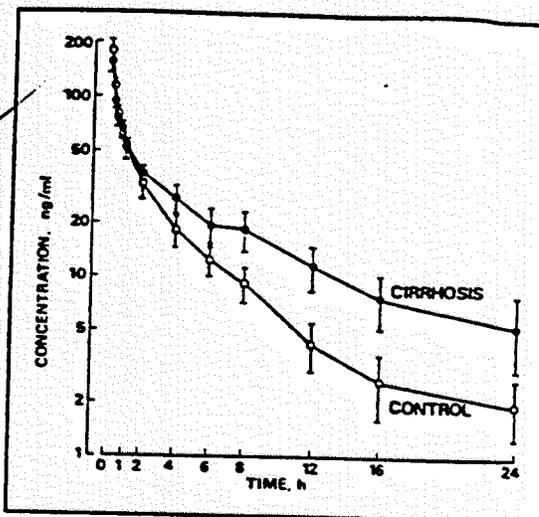


Figure 1. Concentrations of midazolam in plasma following intravenous administration of midazolam to 7 patients with cirrhosis of the liver and to 7 healthy volunteers. Mean \pm SEM.

Statistical Methods

The pharmacokinetics determined in the patients and in the healthy volunteers were compared using Student's *t*-test. Correlations between the pharmacokinetic variables of midazolam and antipyrine were examined using linear regression analysis.

RESULTS

Antipyrine Test

Antipyrine clearance was significantly ($P < 0.001$) decreased in the patients with cirrhosis of the liver, being on average only 34% of the value found in the healthy volunteers (Table I). The elimination half-life of antipyrine in cirrhotic patients was on average about three times that in control subjects (Table I).

Pharmacokinetics of Intravenous Midazolam

The mean serum concentration-time curves of midazolam in cirrhotic and control subjects are presented in Figure 1 and the pharmacokinetic variables in Tables II and III.

Midazolam kinetics in healthy subjects could be adequately described using a two-compartment open model. It was characterized by distribution in a rather large volume, as indicated by high values

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TABLE II

Model-Independent Pharmacokinetic Parameters Obtained After Intravenous Administration of Midazolam* to 7 Patients With Hepatic Cirrhosis and 7 Healthy Volunteers			
Parameter	Cirrhotic Patients	Healthy Volunteers	P
AUC ($\mu\text{g} \cdot \text{h} \cdot \text{l}^{-1}$)	543 \pm 93*	298 \pm 25	<0.05
CL (ml/min/kg)	3.34 \pm 0.60	5.63 \pm 0.43	<0.01
$t_{1/2\alpha}$ (h)	0.41 \pm 0.09	0.31 \pm 0.05	N.S.
$t_{1/2\beta}$ (h)	7.36 \pm 1.22	3.80 \pm 0.61	<0.05
Protein binding, unbound fraction (%)	3.16 \pm 0.82	1.68 \pm 0.37	N.S.

* Dose 8.35 mg of midazolam hydrochloride (7.5 mg as base); *SEM.

both of V_1 and V_{ss} . Elimination occurred predominantly during the β -phase, which accounted for approximately 79% of the AUC, and had a half-life of 3.80 ± 0.61 (SEM) h.

The distribution of midazolam in patients with cirrhosis of the liver did not change from that found in healthy volunteers; $t_{1/2\alpha}$, V_1 and V_{ss} did not differ significantly from the values found in healthy controls. However, the elimination of midazolam was slower in cirrhotic patients as shown by a significantly ($P < 0.01$) reduced total clearance, which averaged 59% of the control value. The total elimi-

TABLE III

Pharmacokinetic Parameters of the Two-compartment Model Describing the Disposition of Intravenous Midazolam* In 7 Patients with Cirrhosis of the Liver and 7 Healthy Volunteers			
Parameter	Cirrhotic Patients	Healthy Volunteers	P
A (ng/ml)	133 \pm 26	159 \pm 23	N.S.
B (ng/ml)	39.8 \pm 4.8	46.3 \pm 9.6	N.S.
α (h^{-1})	2.60 \pm 0.77	2.75 \pm 0.55	N.S.
β (h^{-1})	0.412 \pm 0.086	0.207 \pm 0.024	<0.05
k_{10} (h^{-1})	0.400 \pm 0.063	0.721 \pm 0.076	<0.01
k_{12} (h^{-1})	1.632 \pm 0.658	1.438 \pm 0.344	N.S.
k_{21} (h^{-1})	0.687 \pm 0.132	0.800 \pm 0.180	N.S.
V_1 (l/kg)	0.595 \pm 0.083	0.529 \pm 0.068	N.S.
V_{ss} (l/kg)	1.19 \pm 0.19	1.41 \pm 0.09	N.S.

* Dose 8.35 mg midazolam hydrochloride (7.5 mg as base); * SEM.

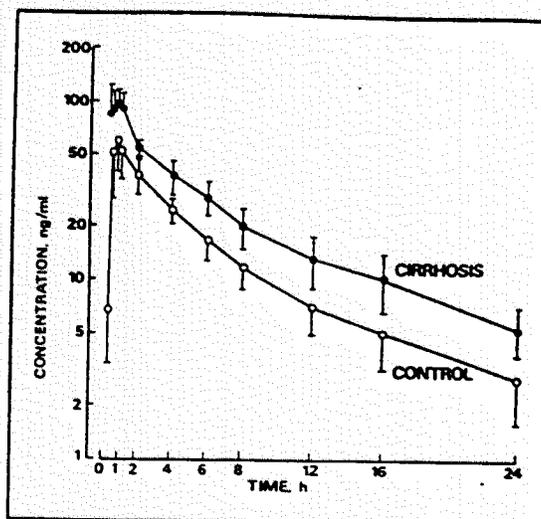


Figure 2. Concentrations of midazolam in plasma following oral administration of midazolam to 6 patients with cirrhosis of the liver and to 7 healthy volunteers. Mean \pm SEM.

nation rate constant (k_{10}) too, was significantly ($P < 0.01$) lower in cirrhotic than in control subjects. The mean elimination half-life of midazolam in the cirrhotic patients was about two times that in the control subjects ($P < 0.05$).

The binding of midazolam to plasma proteins did not differ significantly between patients with cirrhotic and control subjects (Table II).

There was a statistically significant linear correlation between the elimination half-lives of antipyrine and midazolam ($r = 0.755$, $P < 0.01$; Figure 3), and between the total clearances of both drugs ($r = 0.680$; $P < 0.01$).

Pharmacokinetics of Oral Midazolam

The plasma concentrations after the oral administration of midazolam to cirrhotic and control subjects are presented in Figure 2 and the pharmacokinetic variables in Table IV. In healthy subjects the elimination half-life ($t_{1/2\beta}$) was significantly ($P < 0.01$) longer after oral than after intravenous administration, 6.28 ± 0.88 vs. 3.80 ± 0.61 h respectively. The comparison of the AUC values after oral and intravenous administration revealed a mean systemic availability for oral midazolam of $38 \pm 6\%$.

In cirrhotic patients the mean peak plasma concentration of midazolam was on average 43% higher than that in the healthy controls. However, because of the wide interindividual variation the difference

was not statistically significant. The time to peak concentration and the lag-time were similar in both groups. The systemic availability in cirrhotic patients was $76 \pm 14\%$, significantly ($P < 0.05$) higher than the control value.

Hypnotic Effect

After intravenous midazolam both the healthy volunteers and cirrhotic subjects fell asleep in less than 5 minutes and after oral administration within 1 hour. The sleeping time of the healthy volunteers was 1-3 hours after intravenous and 2-3 hours after oral administration. The corresponding figures in the cirrhotic patients were 1-3 hours after both routes of administration.

DISCUSSION

These results indicate that hepatic cirrhosis causes significant changes in the pharmacokinetics of midazolam, characterized by a decrease in total clearance and an increase in both elimination half-life and systemic availability of oral midazolam, whereas the rate of distribution and apparent volume of distribution remain unchanged.

The pharmacokinetics of midazolam after both intravenous and oral administration to healthy volunteers were broadly similar to those previously reported for midazolam in healthy subjects. The total plasma clearance of midazolam was reported to be 7.75 ± 0.41 ml/min/kg in young men (average 28 years) and 4.41 ± 0.68 ml/min/kg in elderly men (average 68 years).¹² The value of 5.58 ± 1.33 ml/min/kg found in the present study was between these values, as was the age of our control subjects (average 43 years). However, the elimination half-life ($t_{1/2\beta}$) found in the present study (3.80 ± 0.61 h) was clearly longer than the half-life found in young men (1.70 ± 0.11 h) but similar to the value reported for elderly men.¹² The long half-life in the present study was obviously caused by a rather large volume of distribution (V_m), which averaged 1.69 ± 0.19 l/kg. The values previously reported for healthy young and elderly men were 1.34 ± 0.08 and 1.64 ± 0.14 l/kg, respectively.¹² The volume of distribution of midazolam has been reported to be larger in obese subjects (up to 2.66 ± 0.16 l/kg).¹² The mean body weight of our control subjects (79 kg) exceeded ideal body weight. Obviously the large volume of distribution and relatively long elimination half-life were related to the high body weight and obesity of most of the control subjects. The absolute systemic availability in the healthy subjects was 38%, which is in agreement with previous findings.¹³⁻¹⁶

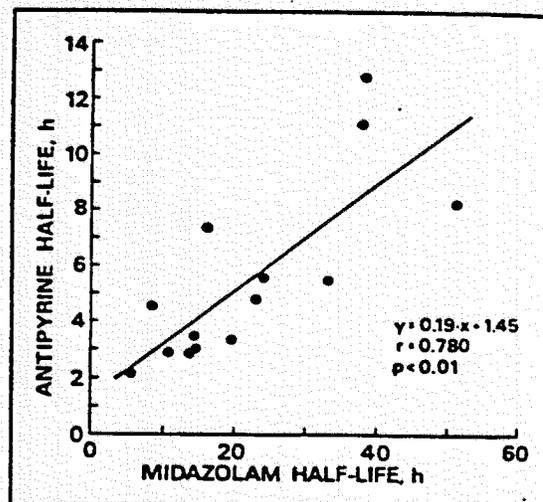


Figure 3. Linear regression for antipyrine half-life versus midazolam half-life.

Midazolam can be classified as a drug of intermediate extraction with high plasma protein binding and elimination largely by hepatic metabolism.¹⁷ The rather low systemic availability of oral midazolam is most likely due to presystemic clearance of the drug. The effects of cirrhosis of the liver on the pharmacokinetics of this type of drug would be a decrease in hepatic extraction, resulting in increased systemic availability and decreased systemic clearance.¹⁸ On the other hand, antipyrine is a flow-insensitive or capacity-limited drug with low hepatic extraction, low plasma protein binding and elimination by hepatic metabolism.¹⁹ The effect of

TABLE IV

Pharmacokinetic Parameters Obtained After Oral Administration of Midazolam* to 6 Patients With Cirrhosis of the Liver and 7 Healthy Volunteers

Parameter	Cirrhotic Patients	Healthy Volunteers	P
C_{max} ($\mu\text{g/l}$)	$129 \pm 24^*$	90 ± 14	N.S.
t_{max} (h)	0.63 ± 0.11	1.22 ± 0.44	N.S.
AUC ($\mu\text{g} \cdot \text{h} \cdot \text{l}^{-1}$)	576 ± 89	362 ± 61	N.S.
$t_{1/2\beta}$ (h)	5.97 ± 1.16	6.28 ± 0.88	N.S.
F (%)	76 ± 14	38 ± 6	<0.05
Lag time (h)	0.30 ± 0.05	0.33 ± 0.07	N.S.

* Dose 20.3 mg of midazolam maleate (15 mg as base); *SEM.

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cirrhosis of the liver on the pharmacokinetics of this type of drug is a decrease in clearance reflecting impaired intrinsic metabolic capacity of the liver. The findings in the present study with cirrhotic patients confirm these theoretical predictions concerning both drugs.

The principal pharmacokinetic change of midazolam in patients with hepatic cirrhosis was a decrease in total plasma clearance. The prolongation of elimination half-life was a consequence of this change, since the volume of distribution remained unchanged.

The oral systemic availability of midazolam was increased about two-fold as compared with the control value, i.e. relatively more than the clearance was decreased in the cirrhotic patients. When the hepatic extraction ratio is high a small decrease in extraction typically results in this pattern of pharmacokinetic consequences.¹⁹ The high peak plasma concentration after oral intake of midazolam may augment the pharmacodynamic effects of midazolam, especially in patients with advanced hepatic cirrhosis, even if this was not obvious in the present study. On a pharmacokinetic basis a reduction in the oral dose of midazolam by about one-half is suggested for these patients.

We have found only one study in the literature in which midazolam kinetics have been evaluated in cirrhotic patients.²⁰ In that study an oral dose of 15 mg of midazolam was given to six patients with hepatic cirrhosis. The pharmacokinetics found resembled those reported in the literature for healthy subjects. However, actual controls were not used, midazolam was not given intravenously, and the degree of liver function impairment was less than in the present study. Nevertheless, the C_{max} values (141 ± 41 [SD] ng/ml) and the AUC-values (438 ± 244 ng·h·ml⁻¹) were close to the present findings.

A statistically significant correlation was found between the respective half-lives and clearances of midazolam and antipyrine. Both drugs are almost completely metabolized to hydroxylated derivatives. Thus, this correlation is not surprising. The elimination of antipyrine was, however, relatively more affected than that of midazolam. This may relate to the different contribution of liver blood flow to the kinetics of these two drugs. It is likely that liver blood flow was relatively better preserved in the patients with cirrhosis than was the intrinsic metabolic capacity of the liver.

In conclusion, the pharmacokinetic changes caused by advanced liver cirrhosis on the pharmacokinetics of midazolam were characterized by an increase in oral systemic availability and by a decrease in clearance with consequent prolongation of elimination half-life. On a pharmacokinetic basis a re-

duction in oral doses of midazolam is suggested for patients with advanced hepatic cirrhosis.

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