CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-038	**Code: 1S**
Name: ——— .™ (Dexmedetomidine HCL) for Infusion	
Sponsor: Abbott Laboratories, 200 Abbott Park, Abbott Park, IL 60064	
Submission Type: Original NDA	**Submission Date:** December 18, 1998
Reviewer: Suresh Doddapaneni, Ph.D.	

SYNOPSIS

Dexmedetomidine is intended for alpha$_2$ sedation and analgesia in an intensive care setting (IC) and is claimed to produce titratable, predictable sedation, from which patients are easily arousable and cooperative.

Chiral inversion of dexmedetomidine to the inactive *levo* isomer is likely to be insignificant. Recovery of the radiolabel in the mass balance study was complete and quantitative. The excretion of the radioactivity was rapid with about 85% recovered in the urine within 24 hours post dosing. Dexmedetomidine undergoes complete biotransformation *in vivo* with very little excreted unchanged in the urine or feces. Biotransformation involves both direct glucuronidation as well as cytochrome P450 mediated metabolism. Direct N-glucuronidation to the inactive G-DEX-1 and G-DEX-2 conjugates accounts for about 34% of its metabolism. Aliphatic hydroxylation of dexmedetomidine (mediated primarily by CYP2A6) to generate 3-hydroxy dexmedetomidine, glucuronide of 3-hydroxy dexmedetomidine, and 3-carboxy dexmedetomidine represents about 14% of the metabolism. N-methylation of dexmedetomidine to generate 3-hydroxy N-methyl dexmedetomidine, 3-carboxy N-methyl dexmedetomidine, and N-methyl O-glucuronide dexmedetomidine accounted for about 18% of the metabolism. Approximately, 28% of the urinary metabolites have not been identified. The average plasma protein binding of dexmedetomidine was 94%. The specific plasma protein to which dexmedetomidine binds is unknown.

Dexmedetomidine exhibits dose-independent pharmacokinetics in the dosage regimen (0.2 to 0.7 µg/kg/hr when infused up to 24 hours) proposed for the indication being sought. The main pharmacokinetic parameter values were consistent across several studies with varied infusion regimens (10 minute infusion, two-stage regimens (loading dose + maintenance dose), three-stage regimens (two loading doses + maintenance dose), and virtually continuously changing infusion rate regimens) and are as follows; The clearance is about 39.0 liter/hr, the terminal half-life is about 2 hours, and the steady state volume of distribution is about 1.3 liter/kg.

Dexmedetomidine did not show gender and age differences in pharmacokinetics of adult subjects. Therefore, based on pharmacokinetic considerations no dosage adjustments are warranted in females or in the elderly.

Dexmedetomidine pharmacokinetics were not affected in patients with severe renal impairment after a single dose administration of dexmedetomidine. No dosage adjustments are warranted based on the results from this study. However, the metabolites are completely excreted

in the urine and it is unknown if the metabolites accumulate when dexmedetomidine is infused continuously.

The pharmacokinetics of dexmedetomidine were affected in hepatic impairment requiring dosage adjustments when dexmedetomidine is used in this patient population. The mean CL values for subjects with mild, moderate, and severe hepatic impairment were only 74%, 64% and 53%, respectively, of those observed in the normal healthy subjects.

Based on *in vitro* metabolism studies, dexmedetomidine is not expected to inhibit the metabolism of drugs whose metabolism is mediated by CYP1A1, CYP1A2, CYP2A6, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 isoforms. *In vivo* interaction studies showed that the pharmacokinetics of dexmedetomidine were not affected by the concurrent administration of alfentanil, midazolam, propofol, and isoflurane. *In vivo* interaction studies also showed that the pharmacokinetics of propofol, midazolam, and rocuronium were not affected by the concurrent administration of dexmedetomidine.

RECOMMENDATION

NDA 21-038 can be approved from the viewpoint of Office of Clinical Pharmacology and Biopharmaceutics provided a mutually acceptable language can be worked out on the clinical pharmacology section of the package insert. Comments 1-2 on page 23 of this review should be sent to the sponsor.

/S/ 1/27/99

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FT initialed by Ramana Uppoor, Ph.D. /S/ 10/99

CC:
NDA 21-038, HFD-170 (Division File, Samantha), HFD-850 (Lesko), HFD-870 (Doddapaneni, Mei-Ling Chen, Uppoor), Barbara Murphy (CDR).

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I. INTRODUCTION

Dexmedetomidine is a potent and highly selective α_2-adrenoceptor agonist (α_2:α_1 ratio of 1600:1). It is the ——— -separated from racemic medetomidine. Activation of alpha$_2$ receptors located in the sympathetic nerve endings inhibits the release of norepinephrine. Activation of postsynaptic receptors by alpha$_2$ agonists in the CNS leads to inhibition of sympathetic activity, decreases in blood pressure and heart rate, sedation, and relief of anxiety. Binding of agonists to alpha$_2$ adrenoceptors in the spinal cord produces analgesia.

Dexmedetomidine is intended for alpha$_2$ sedation and analgesia in an intensive care setting (IC) and is claimed to produce titratable, predictable sedation, from which patients are easily arousable and cooperative. It is claimed to be relatively free of side effects. Most common adverse events associated with its use have been hypotension, hypertension, and bradycardia which are expected extensions of its pharmacologic effect and have been easily managed. Similar proportions of patients have had therapy discontinued because of adverse events in the dexmedetomidine and placebo control groups (3%, 30/1148 dexmedetomidine; 3%, 24/817 placebo). Currently, dexmedetomidine HCl is not approved for marketing in any country.

II. INDICATIONS AND DOSAGE AND ADMINISTRATION AS STATED IN THE PROPOSED PACKAGE INSERT

Indications:

"——— is an alpha$_2$ sedative with analgesic properties for use in an intensive care setting."

Dosage and Administration:

——— should be administered using a controlled infusion device.

——— can be individualized and titrated to the desired clinical effect. For adult patients, ——— is initiated with a loading dose of 1.0 mcg/kg over 10 minutes, followed by a maintenance infusion of 0.2 to 0.7 mcg/kg/hr. The rate of the maintenance infusion should be adjusted to achieve the desired level of sedation and/or analgesia. In clinical studies, doses as low as 0.05 mcg/kg/hr have been used and infusions up to 24 hours have been studied."

III. PHYSICOCHEMICAL PROPERTIES & FORMULATION

Dexmedetomidine is a white or almost white, crystalline powder freely soluble in water with a pKa of 7.1. Dexmedetomidine HCl for Infusion (100 µg/mL as dexmedetomidine base) is presented as a sterile, aqueous solution in ampoules and vials with a pH of 4.5 to 7.0. This solution is preservative free and contains no additive or chemical stabilizers. This solution is further diluted with normal saline prior to intravenous infusion.

IV. DEXMEDETOMIDINE METABOLISM

i. Proposed metabolic pathway

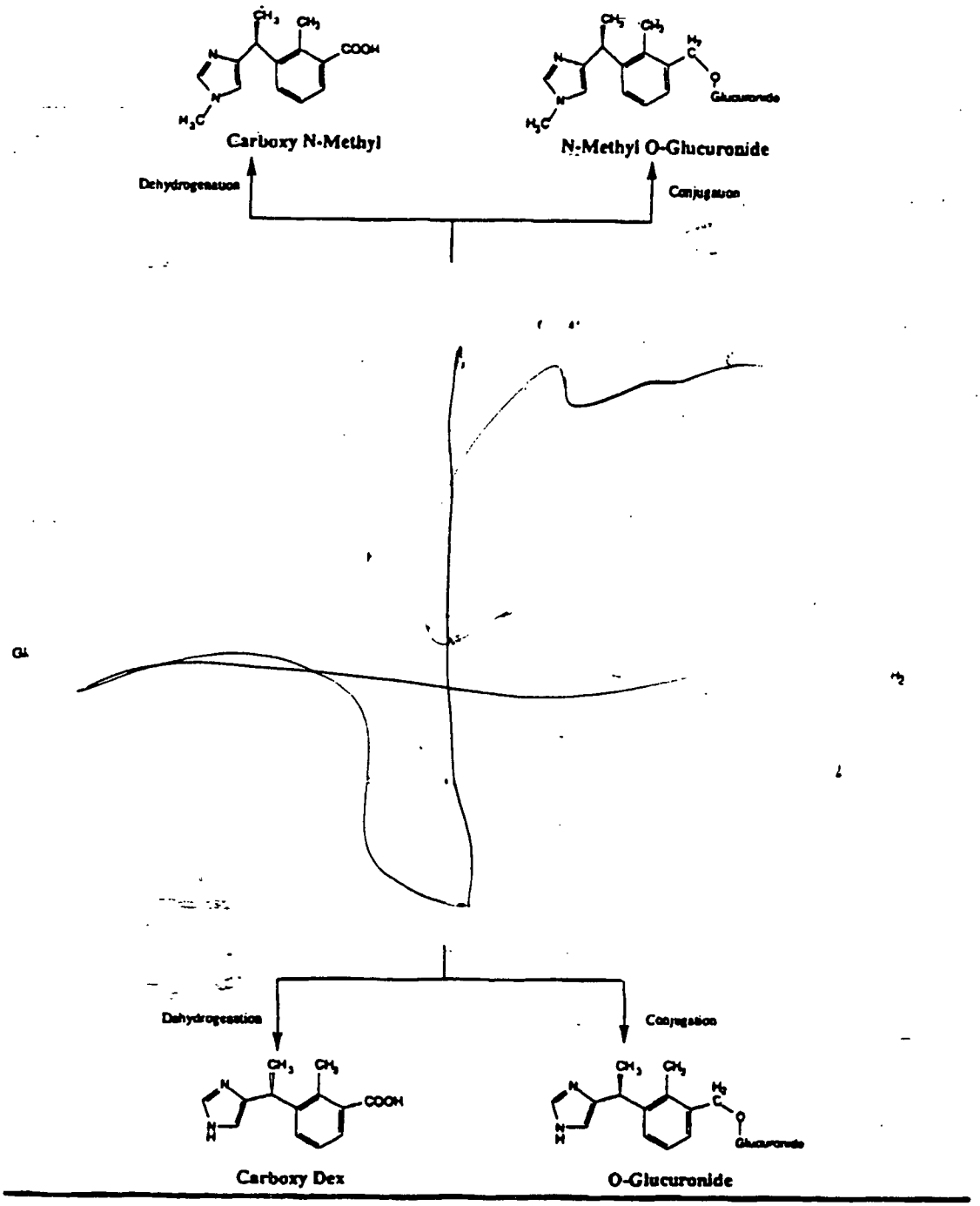
Dexmedetomidine undergoes almost complete biotransformation. No unchanged dexmedetomidine was excreted in urine. Very little (less than 1%) dexmedetomidine was excreted in feces. Biotransformation involves both direct glucuronidation as well as cytochrome P450 mediated metabolism. Figure 1 shows the proposed metabolic pathway of dexmedetomidine. Direct N-glucuronidation to the inactive G-DEX-1 and G-DEX-2 conjugates accounts for about 34% of its metabolism. Aliphatic hydroxylation (mediated primarily by CYP2A6) of dexmedetomidine to 3-hydroxy dexmedetomidine followed by glucuronidation to 3-hydroxy dexmedetomidine glucuronide, and/or further oxidation to 3-carboxylic acid dexmedetomidine represents about 14% of the metabolism. N-methylation of dexmedetomidine followed by aliphatic hydroxylation to 3-hydroxy N-methyl dexmedetomidine, followed further by oxidation to 3-carboxy N-methyl dexmedetomidine, and/or glucuronidation to N-methyl O-glucuronide dexmedetomidine accounts for about 18% of the metabolism. The N-Methyl metabolite itself was a minor circulating component and was undetected in urine. There may be additional uncharacterized metabolites (approximately, 28% of the urinary metabolites have not been identified).

In vitro metabolism studies (using liver microsomes, microsomes containing cDNA-expressed CYP isoforms, and selective CYP2A6 monoclonal antibody) showed that CYP2A6 is the largest single contributor of the CYP mediated hydroxylation of dexmedetomidine. Other isoforms such as CYP1A2, CYP2E1, CYP2D6, and CYP2C19 may also play a role in the hydroxylation of dexmedetomidine (Inhibition by CYP2A6 selective inhibitors was incomplete). *In vitro* metabolism studies also showed that the IC_{50} values for inhibition potential of dexmedetomidine against the different cytochrome P450 isoforms are relatively high compared to the expected therapeutic plasma concentrations of dexmedetomidine. The upper limit of the anticipated therapeutic concentration range is 1.2 ng/mL, which is 0.0096 μM. Based on this, the sponsor is concluding that dexmedetomidine is not likely to inhibit the metabolism and alter the pharmacokinetics of coadministered drugs.

Table 1. IC_{50} values for inhibition potential of dexmedetomidine against the different cytochrome P450 isoforms.

Cytochrome P450 isoform	Substrate	IC_{50} (μM)
1A1	Ethoxyresorufin O-deethylase	2.7
1A2	Ethoxyresorufin O-deethylase	2.0
2A6	Coumarin 7-hydroxylase	70
2C19	S-mephenytoin 4-hydroxylase	3.3
2E1	Chlorzoxazone 7-hydroxylase	2.2
3A4	Testosterone 6β-hydroxylase	0.65
2D6	Dextromethorphan O-demethylase	1.8

Figure 1. Proposed dexmedetomidine metabolic pathway.



ii. Mass Balance

In this study, five (5) healthy male subjects each received a single intravenous infusion of 2 µg/kg [^{3}H]Dexmedetomidine (99% radiochemical purity) over a period of 10 minutes (study DEX-96-018). The majority of radioactivity was excreted into the urine. After nine days, an average of 95% was recovered in the urine with only 4% in the feces. Most of the radioactivity was rapidly excreted since about 85% of the radioactivity recovered in the urine was excreted within 24 hours after the infusion. No unchanged dexmedetomidine was found in the urine or feces.

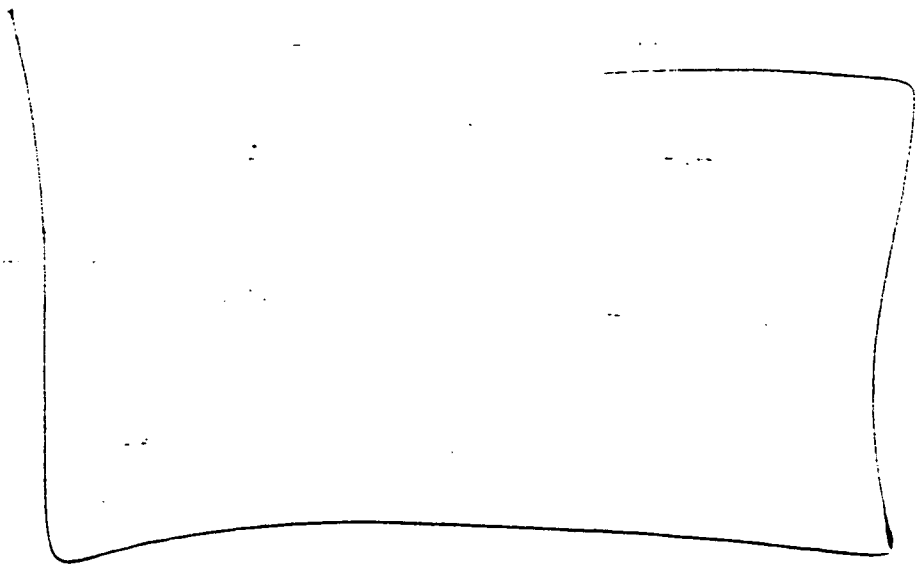
The majority of the plasma total $AUC_{0\text{-}24}$ radioactivity was comprised by dexmedetomidine (14.7%), G-DEX-1 and G-DEX-2 (42%), N-methyl O-glucuronide dexmedetomidine (21%), and H-3, an uncharacterized metabolite (10.5%). Glucuronide of 3-hydroxy dexmedetomidine, 3-carboxylic acid dexmedetomidine, N-methyl dexmedetomidine, and H-2 (uncharacterized) occurred in small quantities ranging from 0.3% to 3.0%. About 6% remained unknown.

Table 2 shows the fractionated cumulative urinary excretion profile of [^{3}H]Dexmedetomidine. N-glucuronide metabolites of dexmedetomidine, G-DEX-1 and G-DEX-2, accounted for about 34% of its cumulative urinary excretion. In addition, aliphatic hydroxylation of dexmedetomidine (3-hydroxy dexmedetomidine, glucuronide of 3-hydroxy dexmedetomidine, and 3-carboxylic acid dexmedetomidine) together represented about 14% of the dose in urine. The N-methyl metabolite itself was a minor plasma circulating component and was undetected in urine. However, N-methylation pathway of dexmedetomidine (3-hydroxy N-methyl dexmedetomidine, 3-carboxy N-methyl dexmedetomidine, and N-methyl O-glucuronide dexmedetomidine) accounted for about 18% of the [^{3}H]dexmedetomidine dose in urine. Approximately, 28% of the urinary metabolites have not been identified.

Table 2. Summary of the Distribution of metabolites in 0-72 hour human urine following a ten minute infusion of 2 µg/kg [^{3}H]Dexmedetomidine in five healthy male volunteers.

Metabolite	% Dose Excreted (Mean (SD))
Dexmedetomidine	0.0 (0.0)
G-Dex1 (N-Glucuronide of dexmedetomidine)	19.6 (3.1)
G-Dex2 (N-Glucuronide of dexmedetomidine)	14.4 (2.5)
OH (3-Hydroxy dexmedetomidine)	1.1 (0.3)
G-OH (Glucuronide of 3-hydroxy dexmedetomidine)	7.7 (0.6)
COOH (3-carboxylic acid dexmedetomidine)	4.8 (1.0)
H-1 (N-Methyl O-glucuronide dexmedetomidine)	14.5 (1.5)
H-4 (N-Methylated carboxylic acid dexmedetomidine)	3.8 (0.7)
Others	28.0 (4.8)
% Dose Excreted	**93.8 (1.6)**

iii. Metabolic Inversion



V. PROTEIN BINDING

Dexmedetomidine plasma protein binding was assessed in the concentration range of [redacted] L (therapeutic concentrations are around 1 ng/mL). The average protein binding was 94% and showed concentration independence. The specific plasma protein to which the drug bounds is unknown.

The protein binding did not change in severe renal impairment but it slightly decreased in hepatic impairment (88% and 82% in mild and severe hepatic impairment groups compared to 90% in normal group). Binding displacement of dexmedetomidine by therapeutic concentrations of fentanyl, ketorolac, theophylline, digoxin, and lidocaine explored *in vitro* did not show any changes in the protein binding of dexmedetomidine. Similarly, dexmedetomidine did not show any changes in the *in vitro* protein binding of therapeutic concentrations of phenytoin, warfarin, ibuprofen, propranolol, theophylline, and digoxin.

VI. PHARMACOKINETICS AND DOSE-PROPORTIONALITY

Originally, dexmedetomidine was pursued as an anesthetic adjunct. Therefore, majority of the studies evaluated the pharmacokinetics of dexmedetomidine after short term infusions. DEX-97-028 is the only study that evaluated the pharmacokinetics of dexmedetomidine simulating the continuous infusion regimen that will be used for sedation in ICU setting. Table 3 provides a summary of clearance values from some of these studies and from study DEX-97-028. This list contains a variety of infusion regimens including 10-minute infusions, two-stage regimens (loading dose + maintenance dose), three-stage regimens (two loading doses + maintenance dose), and virtually continuously changing infusion rate regimens. A computer controlled infusion pump (CCIP) was used to achieve these varying dosing regimens. Overall, mean estimates of

clearance across these different studies ranged from 35 to 43 liter/hour with a central estimate of about 39 liter/hour, irrespective of the nature of the infusion regimen.

Table 3. Dexmedetomidine pharmacokinetic parameters obtained in several different studies.

Study	Study Type	Infusion Type	Dose (µg/kg)	CL (liter/hr)	V_{ss} (liter/kg)	$T_{1/2}$ (hour)
Dex-95-008	Renal* Impairment	10-minute	0.6	41.2	1.31	2.22
DEX-95-009	Hepatic* Impairment	10-minute	0.6	41.9	1.54	2.39
DEX-97-028	Patients	Loading + Maintenance infusion up to 24 hours	18.2/24 hrs	38.8	1.32	2.06
F-DEX-CL-0592-FIN	CABG Patients	Loading + maintenance	2.76	40.0	-	-
DEX-96-013	Age & Gender*	10-minute	0.6	39.3	1.50	2.19
DEX-95-007	Safety*	CCIP#	9.38	35.7	1.16	2.45
DEX-95-011	Interaction with Alfentanil	CCIP#	2.4	38.0	-	-
DEX-96-019	Interaction with Propofol	CCIP#	1.44	41.3	1.71	2.27

* Pharmacokinetic parameters from healthy subjects.
# Computer controlled infusion pump

Study Dex-97-028 evaluated the pharmacokinetics of dexmedetomidine in the dose range of 0.17 to 0.7 µg/kg/hour after continuous infusion for 24 hours supporting the dosage regimen for the ICU sedation indication being sought. This trial was designed as a two-part, Phase 1, placebo-controlled, double-blinded dose-ranging trial in 72 subjects. In part 1, five dose levels targeting 0.1, 0.3, 0.45, 0.6, 1.25 ng/mL pseudo-steady-state plasma concentrations were evaluated after 1-hour infusions. In part 2, dose levels to achieve 0.3, 0.6, and 1.25 ng/mL target plasma concentrations were evaluated after 24 hour infusions. Table 4 shows the corresponding infusion rates for the targeted plasma concentrations used in this study (note: during the initial development process, the doses were given in terms of target plasma concentrations).

Table 4. Maintenance infusion rates and corresponding expected steady state plasma dexmedetomidine concentrations.

Target Steady State Concentrations (ng/mL)	Maintenance Infusion Rates (µg/kg/hour)
0.1	0.06
0.2	0.11
0.3	0.17
0.5	0.28
0.7	0.39
0.9	0.50
1.25	0.70

Figures 2 and 3 present the mean dexmedetomidine concentrations vs. time profile and mean AUC vs. mean dose profile following 1 hour and 24 hour dexmedetomidine infusions, respectively. The mean dexmedetomidine pharmacokinetic parameters after the 24 hour infusions are presented in table 5. In general, the pharmacokinetic parameter values were similar to those values obtained in previous studies. There were no statistically significant differences in clearance or half-lives across the different regimens evaluated in this study. It could be seen from figure 3 and table 5 that there is approximate dose-proportionality in dexmedetomidine therapeutic concentrations when continuously infused for up to 24 hours. The mean AUC versus mean dose plot showed linearity. The average pseudo-steady-state concentrations approximately doubled and the clearance was similar.

Figure 4 shows the mean Ramsay sedation scores vs. dexmedetomidine concentrations plot. Visual inspection of Ramsay sedation plots indicated that the midrange of sedation (Ramsay score of 3.5) was achievable by dexmedetomidine concentrations in the range of 0.3 ng/mL to 0.6 ng/mL and the maximum Ramsay sedation score achieved in the current study appears to be in the range of about 4.5 to 5. Eight individuals achieved a Ramsay score of 6 on at least one assessment.

Table 5. Mean ± SD Pharmacokinetic Parameters, Part II.

Parameter	Loading Infusion (min)/Total infusion duration (hrs)			
	10 min/12 hrs	10 min/24hrs	10 min/24 hrs	35 min/24 hrs
	Dexmedetomidine Target Concentration (ng/mL)			
	0.3	0.3	0.6	1.25
C_{max}, ng/mL	0.87 ± 0.25	1.05 ± 0.17	1.59 ± 0.51	2.40 ± 0.59
$t_{1/2}$*, hour	1.78 ± 0.30	2.22 ± 0.59	2.23 ± 0.21	2.50 ± 0.61
CL, liter/hour	46.3 ± 8.3	43.1 ± 6.5	35.3 ± 6.8	36.5 ± 7.5
V_{ss}, liter	88.7 ± 22.9	102.4 ± 20.3	93.6 ± 17.0	99.6 ± 17.8
Avg Css#, ng/mL	0.27 ± 0.05	0.27 ± 0.05	0.67 ± 0.10	1.37 ± 0.20

* Presented as harmonic mean and pseudo standard deviation.

\# Avg Css = Average steady-state concentration of dexmedetomidine. (2.5 - 9 h samples for 12 hour infusion and 2.5 - 18 h samples for 24 hour infusions.).

Figure 2. Mean dexmedetomidine plasma concentration vs. time profiles after the infusion of dexmedetomidine for 1 hour and 24 hours.

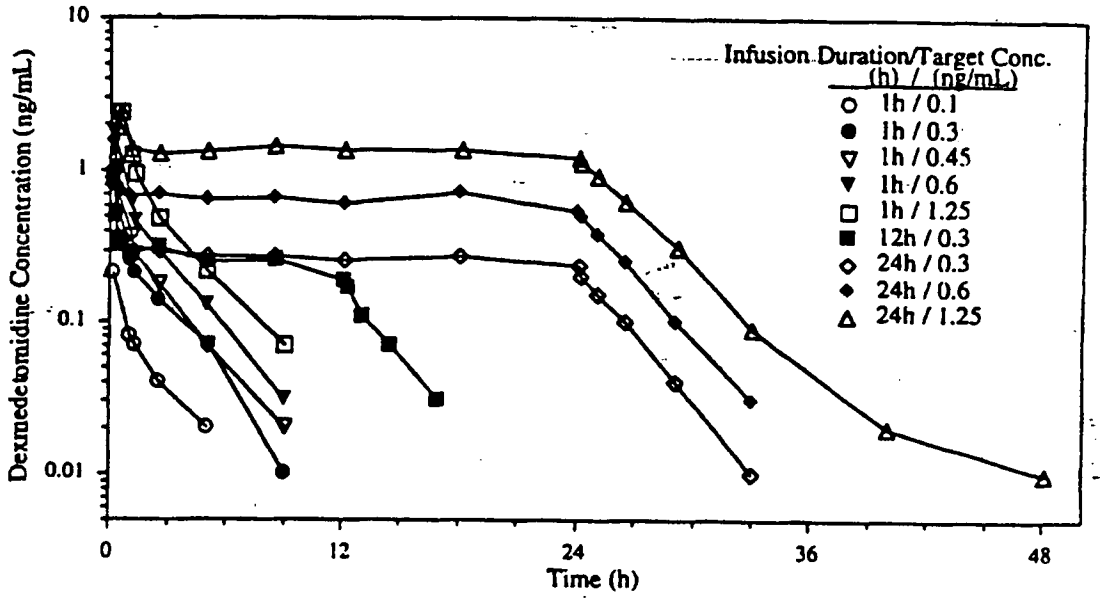


Figure 3. Dexmedetomidine mean AUC vs. mean dose profile.

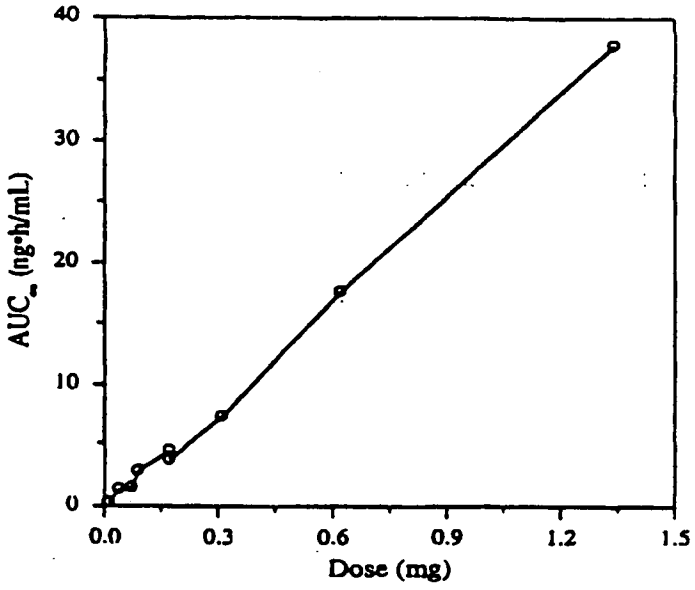
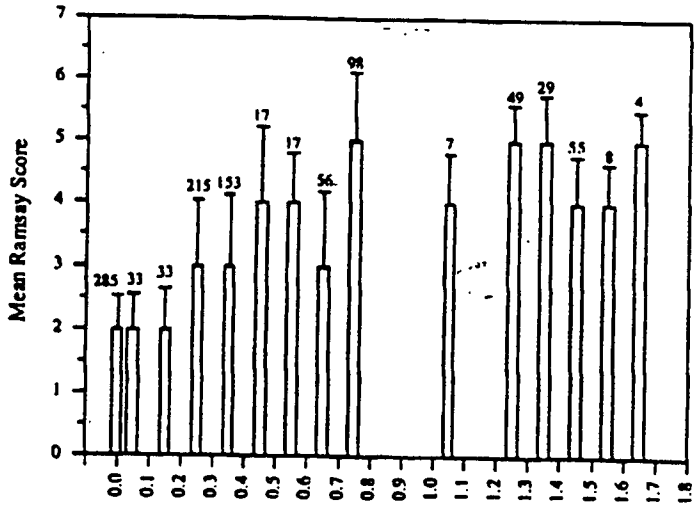


Figure 4. Mean Ramsay sedation scores vs. dexmedetomidine concentrations.



[a] For each Ramsay score, a dexmedetomidine plasma concentration (ng/mL) was linearly interpolated from the surrounding dexmedetomidine values, if not measured. A mean Ramsay score was then calculated for each 0.1 ng/mL increment of dexmedetomidine. Each bar is centered over the mean of the dexmedetomidine increment and represents the mean Ramsay score for that dexmedetomidine concentration range. The number above each bar is the number (N) of Ramsay scores used to compute the mean at that dexmedetomidine concentration range. Bars comprising of less than 4 values were omitted.

VII. SPECIAL POPULATIONS

i. Hepatic Failure

This was a Phase 1, two-center, open-label, single-period, single-dose study in which eighteen (18) normal healthy subjects and six (6) mild impairment, seven (7) moderate impairment and six (6) severe hepatic impairment subjects received an intravenous infusion of 0.6 μg/kg of dexmedetomidine hydrochloride over ten minutes (study DEX-95-009).

Mean dexmedetomidine clearance values were lower in subjects with hepatic impairment than in healthy subjects, which is consistent with the knowledge that dexmedetomidine is eliminated primarily by hepatic metabolism and is highly bound to plasma proteins (table 6). As a result of reduced serum albumin, the fraction of dexmedetomidine that was bound to plasma proteins decreased statistically significantly in subjects with hepatic impairment compared to healthy subjects. The mean clearance values for subjects with mild, moderate, and severe hepatic impairment were only 74%, 64% and 53%, respectively, of those observed in the normal healthy subjects. Compared to the subjects with normal hepatic function

(mean $t_{1/2}$ of 2.5 hours), the mean terminal half-life for the subjects with mild, moderate or severe hepatic impairment were prolonged to 3.9 hours, 5.4 and 7.4 hours, respectively. Therefore, the dose of dexmedetomidine may need to be reduced in subjects with hepatic impairment depending on the degree of impairment.

Table 6. The main mean ± standard deviation of dexmedetomidine pharmacokinetic parameters obtained in normal healthy subjects and subjects with various degrees of hepatic impairment.

Pharmacokinetic parameter	Healthy Subjects	Mild Impairment	Moderate Impairment	Severe Impairment
Fraction bound (%)	89.7 ± 1.6	87.9 ± 0.9	86.5 ± 2.0	82.1 ± 3.8
$t_{1/2}$ (hours)*	2.4 ± 0.5	3.3 ± 1.6	4.6 ± 2.2	7.2 ± 1.8
CL (liter/hour/kg)	0.54 ± 0.18	0.44 ± 0.17	0.34 ± 0.18	0.25 ± 0.03
CL_r (liter/hour)	417.7 ± 160.5	247.9 ± 85.5	211.7 ± 140.6	132.9 ± 34.6
V_{ss} (liter/kg)	1.54 ± 0.55	1.49 ± 0.44	1.31 ± 0.49	2.36 ± 0.49
$V_{ss/f}$ (liter/kg)	1239 ± 489	776 ± 172	741 ± 338	1167 ± 217

* Harmonic mean and pseudo-standard deviation

ii. Renal Failure

This was a Phase 1, two-center, open-label, single-period, single dose study in which six (6) normal healthy subjects and six (6) subjects with severe renal impairment received an intravenous infusion of 0.6 µg/kg of dexmedetomidine-HCl over ten minutes using a computer controlled infusion pump (study DEX-95-008).

There were no statistically significant differences in dexmedetomidine pharmacokinetics between normal healthy subjects and subjects with severe renal impairment (Table 7) consistent with the knowledge that dexmedetomidine undergoes complete biotransformation and is not excreted unchanged in the urine. In addition, no significant associations were observed between dexmedetomidine clearance and creatinine clearance values. Accordingly, for a given administration regimen the pharmacokinetic profile of dexmedetomidine is expected to be independent of the patient's renal function. No data was provided addressing the accumulation of metabolites. It should be noted that since the metabolites of dexmedetomidine are excreted in the urine, they may accumulate in renal impairment subjects (dexmedetomidine for ICU sedation is infused continuously for several hours). The direct N-glucuronide metabolites, G-DEX-1 and G-DEX-2 (accounting for 35% of urinary excretion) were found to be inactive *in vivo* in animal studies. However, the activity of other metabolites excreted in the urine and their potential accumulation when dexmedetomidine is infused continuously for several hours in renal impairment subjects is unknown.

Table 7. The main mean ± standard deviation of dexmedetomidine pharmacokinetic parameters obtained in normal healthy subjects and subjects with severe renal impairment.

Parameter	Normal Subjects	Severe Renal Impairment Subjects
C_{max} (ng/mL)	0.960 ± 0.43	0.833 ± 0.26
$t_{1/2}$ (hour)*	2.22 ± 0.39	2.02 ± 0.25
CL (liter/hour/kg)	0.470 ± 0.11	0.560 ± 0.25
V_{ss} (liter/kg)	1.31 ± 0.26	1.40 ± 0.52

* Harmonic mean and pseudo-standard deviation.

iii. Gender & Elderly

This was a Phase 1, single-center, open label, parallel group study (DEX-96-013) stratified by three age groups with sufficient male and female subjects in each age group to permit gender analysis; 18 to 40 years (9 male, 11 female), 41 to 65 years (14 male, 6 female), and older than 65 years of age (12 male, 8 female). Each subject received a single 10 minute intravenous infusion of 0.6 μg/kg dexmedetomidine-HCl.

Dexmedetomidine pharmacokinetics were not different between young, middle-age and elderly adult subjects (table 8). Therefore, the same dexmedetomidine infusion is expected to produce the same dexmedetomidine concentration profile and the elimination characteristics are expected to be the same irrespective of age.

Dexmedetomidine pharmacokinetics were not different between male and female subjects, when differences in body weight were accounted for. Therefore, the same dexmedetomidine infusion is expected to produce the same dexmedetomidine concentration profile and the elimination characteristics are expected to be the same for men and women.

Table 8. The main mean ± standard deviation of dexmedetomidine pharmacokinetic parameters obtained in subjects with different age groups.

Parameter	18-40 years	41-65 years	>65 years
C_{max} (ng/mL)	1.48 ± 0.28	1.62 ± 0.28	1.5 ± 0.29
$t_{1/2}$ (hour)*	2.11 ± 0.48	2.18 ± 0.34	2.28 ± 0.35
CL (liter/hour)	38.1 ± 8.7	41.2 ± 10.1	38.7 ± 9.1
V_{ss} (liter/kg)	1.19 ± 0.24	1.13 ± 0.17	1.29 ± 0.23

* Harmonic mean and pseudo-standard deviation

iv. Pediatrics

The pharmacokinetics of dexmedetomidine have not been characterized in children. The sponsor is proposing the following statements in the package insert regarding this issue:

"The pharmacokinetic profile [redacted] has not been studied in children".

"Safety and efficacy of [redacted] in children below 18 years of age have not been established".

Per this reviewer's request on the sponsor's pediatric pharmacokinetic study plans, the sponsor through a fax dated 9/16/99 informed that pediatric pharmacokinetic data will be obtained from the ongoing study W98-266. Final reports of this study may be available in mid-2000.

v. Maternal/Fetal Ratio

No adequate and well-controlled studies have been conducted in pregnant women or in labor and delivery. Therefore, no pharmacokinetic information is available in these populations. The sponsor is proposing the following statements in the package insert regarding these patient populations:

"There are no adequate and well-controlled studies in pregnant women. [redacted] should be used during pregnancy only if the potential benefits justify the potential risk to the fetus."

"The safety [redacted] in labor and delivery has not been studied and is, therefore, not recommended for obstetrics, including cesarean section deliveries."

vi. Drug-Drug Interactions

The IC_{50} values for inhibition potential of dexmedetomidine against the different cytochrome P450 isoforms are relatively high compared to the expected therapeutic plasma concentrations of dexmedetomidine (see section IV.i, page 5 of this review). Based on this, the sponsor is concluding that dexmedetomidine is not likely to inhibit the metabolism and alter the pharmacokinetics of coadministered drugs. In addition, pharmacokinetic data was obtained from several studies conducted to examine the clinical effects when dexmedetomidine was coadministered with isoflurane (CYP2E1 substrate), rocuronium, alfentanil (CYP 3A4 substrate), propofol, and midazolam (CYP3A4 substrate). However, it is possible that inducers/inhibitors of CYP2A6, the major isoform involved in the metabolism of dexmedetomidine, may affect dexmedetomidine metabolism. No formal drug-drug interactions were conducted examining the affect of CYP2A6 inducers or inhibitors on dexmedetomidine metabolism.

a) Isoflurane

This was a phase I, single center, randomized, single blind, three-way crossover, controlled study to determine the effects of dexmedetomidine on isoflurane requirements in ten (10) healthy volunteers (study Dex-95-001). Subjects received infusions of placebo or pseudo-steady-state dexmedetomidine target concentrations of 0.3 ng/mL or 0.6 ng/mL for two hours prior to receiving isoflurane anesthesia.

There were no statistically significant differences in any of the main pharmacokinetic parameters of dexmedetomidine between the two target concentrations of 0.3 ng/mL and 0.6 ng/mL (table 9) indicating that isoflurane did not affect the pharmacokinetics of dexmedetomidine.

Table 9. The main mean ± standard deviation of dexmedetomidine pharmacokinetic parameters obtained after isoflurane administration.

Parameter	0.3 ng/mL Target Concentration	0.6 ng/mL Target Concentration
Css (ng/mL)#	0.352 ± 0.46	0.729 ± 0.106
$t_{1/2}$ (hour)*	1.86 ± 0.39	1.94 ± 0.14
CL (liter/hour/kg)	0.52 ± 0.06	0.495 ± 0.09
V_{ss} (liter/kg)	1.47 ± 0.46	1.33 ± 0.19

* Harmonic mean and pseudo-standard deviation.

average of concentrations measured between 2 hours and end of infusion.

b) Midazolam

This was a single-centre, double-blind, randomized, placebo controlled, three-period, cross-over study in nineteen (19) healthy volunteers (study DEX-95-005). Dexmedetomidine or placebo was administered as a loading infusion given for 10 minutes followed by a maintenance infusion of up to 12 hours, targeting dexmedetomidine steady-state plasma levels of 0.0 ng/mL, 0.2 ng/mL or 0.4 ng/mL. Midazolam was administered stepwise using a CCIP 2 hours after the start of the dexmedetomidine infusion. Each step consisted of two stages, a 5 minute loading infusion followed by a 20 minute maintenance infusion. In the eleven steps, maintenance infusions ranged from 4.35 µg/kg/hr to 250.84 µg/kg/hr.

For dexmedetomidine, the clearance was similar at the two target concentrations of 0.2 ng/ml and 0.4 ng/mL (41.4 and 39.1 liter/hour, respectively) indicating that midazolam did not have any affect on dexmedetomidine pharmacokinetics. Similarly for midazolam, the clearance was similar when coadministered with placebo, 0.2 ng/mL or 0.4 ng/mL target dexmedetomidine regimen (32.6, 32.1, 31.4 liter/hour, respectively) indicating that dexmedetomidine did not have any affect on midazolam pharmacokinetics.

c) Propofol

This was a randomized, double blind, two-period crossover, study in ten (10) healthy volunteers (DEX-96-019). Subjects received infusions of placebo or pseudo-steady-state dexmedetomidine target concentration of 0.5 ng/mL for up to three hours. Forty five minutes after the start of dexmedetomidine infusion, propofol infusion was initiated with a CCIP in a manner designed to achieve a stepwise logarithmically ascending concentration profile. Propofol target concentrations ranged from 1 µg/mL at step 1 to 13.79 µg/mL at step 11. Each propofol step lasted 10 minutes.

Dexmedetomidine pharmacokinetic parameters in this study after propofol administration were similar to those observed in other studies (table 10). Propofol

pharmacokinetics were similar between placebo infusion and dexmedetomidine infusion indicating that dexmedetomidine did not have an effect on propofol pharmacokinetics.

Table 10. The main mean ± standard deviation of dexmedetomidine and propofol pharmacokinetic parameters.

Parameter	Dexmedetomidine	Propofol	
		Placebo Treatment	Dexmedetomidine Treatment
$t_{1/2}$ (hour)*	2.27 ± 0.46	2.33 ± 0.7	2.27 ± 0.82
CL (liter/hour)	41.5 ± 8.15	119 ± 22.4	124 ± 46.8
V_{ss} (liter/kg)	1.71 ± 0.19	3.93 ± 0.82	3.53 ± 1.36

* Harmonic mean and pseudo-standard deviation.

d) Rocuronium

This was an open-label study in ten healthy male and female volunteers designed to evaluate the effect of dexmedetomidine on the level of rocuronium-induced muscle relaxation. After stable anesthesia was achieved using alfentanil and propofol, rocuronium administration began at an initial infusion rate of 200 µg/kg/hour. It was then adjusted to maintain a stable T1 at 50% of the baseline value. After stabilization of neuromuscular block, dexmedetomidine was administered to achieve a steady concentration of 0.6 ng/mL using a CCIP. After 45 minutes of dexmedetomidine infusion, all infusions were stopped.

No statistically significant difference was found between the rocuronium concentrations immediately before the start of dexmedetomidine infusion and concentrations 15 and 30 minutes later. However, there was a significant difference for the comparison of pre-dexmedetomidine rocuronium concentrations and those 45 minutes later. It should be noted that the elapsed time from last change in rocuronium infusion rate until dexmedetomidine infusion began ranged from 10-24 minutes meaning that rocuronium with a terminal half-life of 71 minutes will not achieve new steady state concentrations within the 45 minutes of dexmedetomidine infusion. This is reflected in the small rise in rocuronium concentrations during the 45 minutes of dexmedetomidine infusion (Table 11). The small but statistically significant difference between concentrations of rocuronium prior to dexmedetomidine infusion as compared to 45 minutes after the start of dexmedetomidine may be due to rocuronium not having achieved steady-state (1.66 versus 1.79 ng/mL). The overall conclusion from this study was that dexmedetomidine does not affect the pharmacokinetic parameters of rocuronium. The study design employed in this study did not permit the evaluation of the affect of rocuronium on dexmedetomidine pharmacokinetics.

Table 11. Mean dexmedetomidine and rocuronium concentrations.

Time After Start of Dexmedetomidine Administration (minutes)	Dexmedetomidine Concentrations (ng/mL)	Rocuronium Concentrations (ng/mL)
0	0.002 ± 0.005	1.66 ± 0.29
15	1.03 ± 0.15	1.73 ± 0.37
30	0.96 ± 0.15	1.78 ± 0.43
45	0.94 ± 0.14	1.79 ± 0.41

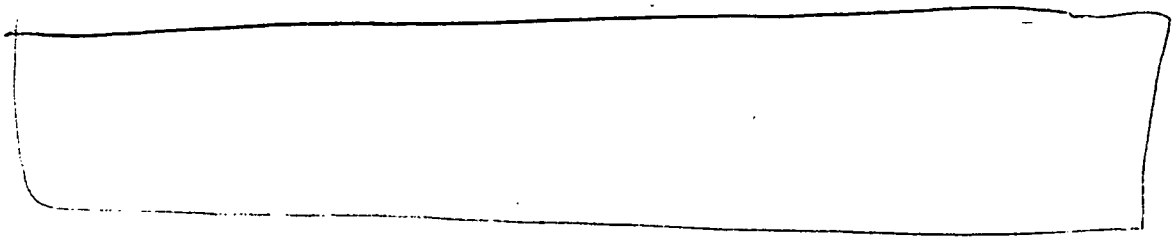
e) Alfentanil

This was a randomized, placebo controlled, three-period crossover study in which 9 healthy male subjects participated (study DEX-95-011). The volunteers received intravenous infusions of placebo or dexmedetomidine using a computer controlled infusion pump (CCIP) to achieve and maintain target steady state plasma concentrations of 0, 0.3 or 0.6 ng/mL for up to 6.75 hours. Forty five minutes later, alfentanil was infused with a second CCIP, in a manner designed to achieve a stepwise logarithmically ascending alfentanil concentration profile. Each alfentanil step lasted 30 minutes.

The overall mean dexmedetomidine clearance in the current study was 38.0 liter/hour, a value similar to those obtained in previous studies. Clearances for the two regimens differed with the lower clearance of 33 liters/hour associated with higher pseudo-steady-state mean concentrations of 0.86 ng/mL. The low dose regimen was associated with a higher clearance of 42.8 liters/hour and pseudo-steady-state concentration of 0.358 ng/mL. Average pseudo-steady-state concentrations achieved in the two regimens were greater than the intended or targeted concentrations because the clearance used to drive the CCIP was higher than the clearance estimated in the current study.

Alfentanil AUC estimates, computed from zero through the last step for which data was available in all treatment groups, on a subject-by-subject basis, indicated a 7% greater area as compared to the placebo regimen, irrespective of low or high dexmedetomidine regimen indicating that dexmedetomidine does not significantly influence the pharmacokinetics of alfentanil.

VIII. ANALYTICAL METHODOLOGY

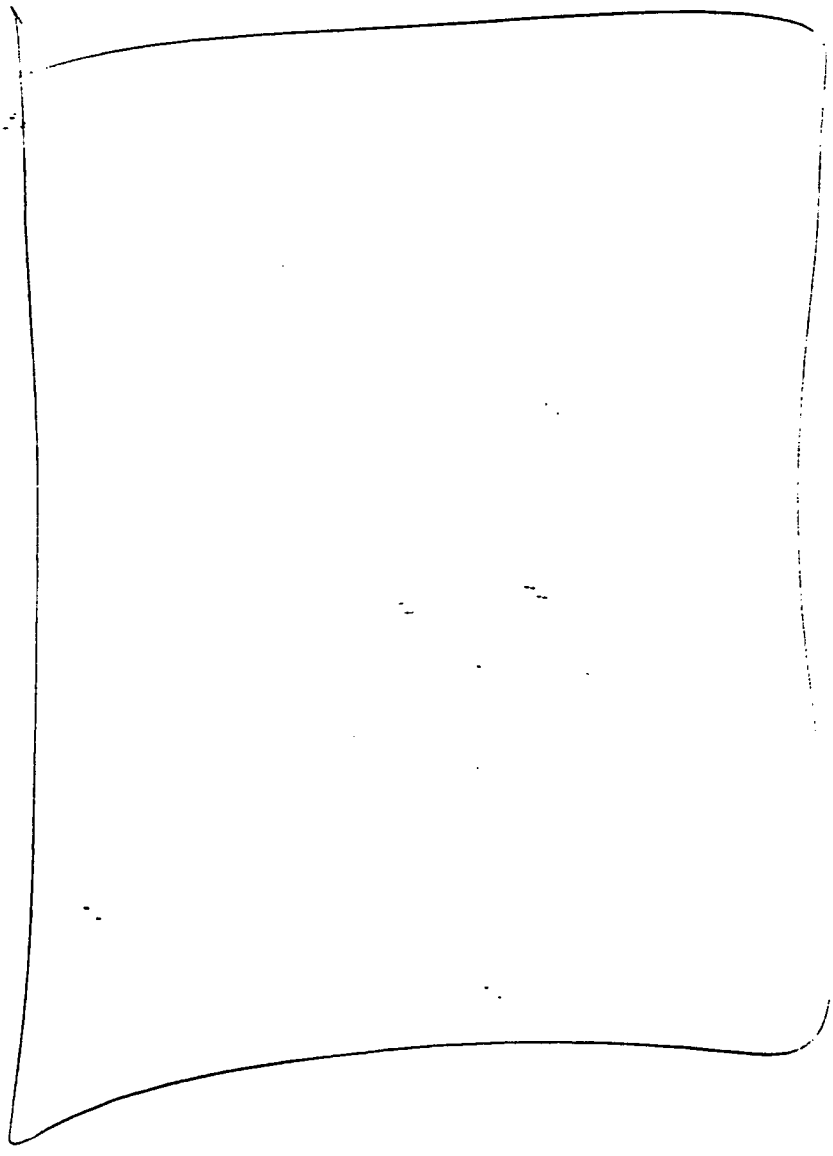


IX. CONCLUSIONS

1. Chiral inversion pathway of dexmedetomidine to the inactive *levo* isomer is likely to be of little significance.
2. Most of the radioactivity in the mass balance study was rapidly excreted since about 85% of the radioactivity recovered in the urine was excreted within 24 hours after the infusion. No unchanged dexmedetomidine was found in the urine or feces.
3. The major metabolic pathways of dexmedetomidine are: direct N-glucuronidation to G-DEX-1 and G-DEX-2; aliphatic hydroxylation of dexmedetomidine to generate 3-hydroxy dexmedetomidine, glucuronide of 3-hydroxy dexmedetomidine, and 3-carboxy dexmedetomidine; N-methylation of dexmedetomidine to generate 3-hydroxy N-methyl dexmedetomidine, 3-carboxy N-methyl dexmedetomidine, and N-methyl O-glucuronide dexmedetomidine.
4. CYP2A6 appears to be the major isoform involved in the metabolism of dexmedetomidine, although other isoforms such as CYP1A2, CYP2A6, CYP2E1, CYP2D6, and CYP2C19 may be involved.
5. The average plasma protein binding was 94%. The specific plasma protein to which dexmedetomidine binds is unknown.
6. The main pharmacokinetic parameters of dexmedetomidine were consistent across the studies regardless of the dosage regimen. After continuous infusion of dexmedetomidine for 24 hours, the clearance, steady state volume of distribution and terminal half-life values were 39 liter/hour, 1.32 liters/kg, and 2.06 hours, respectively. Dose-proportionality was seen in the dosage regimen proposed in the package insert. ✓
7. There were no statistically significant differences in dexmedetomidine pharmacokinetics between normal healthy subjects and subjects with severe renal impairment. ✓
8. Dexmedetomidine pharmacokinetics were not different between young, middle-age and elderly adult subjects. what about PD... titration ?
9. Dexmedetomidine pharmacokinetics were not different between male and female subjects, when differences in body weight were accounted for.
10. Dexmedetomidine pharmacokinetics were altered significantly in hepatic impairment subjects and would require dosage adjustments when used in these patients. The mean CL values for subjects with mild, moderate, and severe hepatic impairment were only 74%, 64% and 53%, respectively, of those observed in the normal healthy subjects.
11. Based on *in vitro* metabolism studies, dexmedetomidine is not expected to inhibit the metabolism of drugs whose metabolism is mediated by CYP1A1, CYP1A2, CYP2A6, CYP2C19, CYP2D6, CYP2E1, CYP3A4 isoforms.

12. *In vivo* interaction studies showed that the pharmacokinetics of dexmedetomidine were not affected by the concurrent administration of alfentanil, propofol, midazolam and isoflurane.

13. *In vivo* interaction study showed that the pharmacokinetics of rocuronium, alfentanil, midazolam, and propofol were not affected by the concurrent administration of dexmedetomidine.



XII. APPENDIX

MASS BALANCE

Study Type: Mass Balance

Study Title: Phase I study of the Metabolism and Excretion of [3H]Dexmedetomidine HCl (Abbott-85499.1) in Normal Male Subjects.

NDA: 21-038 Submission Date: 12/18/98 Volume: 1.48 Protocol: Dex-96-018

Clinical Investigator: J. Broekhuysen, Ph.D., Bio-Pharma S.A., Belgium.

Analytical Investigator: J. Broekhuysen, Radioisotope Laboratory of Biopharma S.A., Belgium.

Subject Breakdown
Normal Yes N= 5 M= 5
Weight Mean 76 kg Range 72-87 kg

Formulation

Treatment Group	Dose	Dosage Form	Strength	Lot
-	2.01 µg/kg	Sterile Solution	2.01 µg/kg	55585-ST-37 (labeled) & 15-096VH (unlabeled)

Analytical Methodology

[redacted]

Labeling Claims
None

Results and Discussion

Five healthy male subjects each received a single intravenous infusion of 2 µg/kg [^{3}H]Dexmedetomidine [redacted] over a period of 10 minutes. One of the five subjects was a slow metabolizer of dextromethorphan indicating a deficiency of CYP 450 2D6. However, this subject did not seem to differ significantly from the other four in the metabolic pathways.

The drug related tritium concentrations in whole blood taken at 0.25, 1.5, 6, and 12 hours post dosing showed that mean levels in blood were 56% of those found in respective

plasma samples. The cell to plasma ratios rang _____ time points indicating virtually no penetration of drug related radioactivity into the cellular fraction.

The plasma concentration time profile of radioactivity is shown in figure 2. The pattern was similar in all five subjects. The highest mean levels (3.18 ng Eq/g) occurred at the end of the 10 minute infusion. This level fell to 0.63 ng Eq/g by 12 hours and 0.20 ng Eq/g by 24 hours. Between 1.5 and 2 hours, there was a second peak corresponding with the appearance of metabolites. The radioactivity declined very slowly thereafter (0.02 ng Eq/g on day 9 and 0.01 on day 23/24) resulting in an overall mean elimination half-life of 10.6 days for total radioactivity. This value is in good agreement with the half-life of tritiated water in humans (9.5 days). However, due to the very low levels of radioactivity in the day 23/24 plasma, the contribution of tritiated water to the total radioactivity could not be determined. However, it should be noted that mean plasma levels of tritiated water represented less than 1% of the plasma total radioactivity up to 8 hours before comprising 43% at the end of day 9. The proposed metabolic pathway for dexmedetomidine is shown in figure 1. Fraction of plasma radioactivity showed that the following compounds were present: dexmedetomidine, G-DEX-1, G-DEX-2, glucuronide of N-methylated hydroxy metabolite, H-3 (uncharacterized), COOH, G-OH, the N-methyl, H-2 (uncharacterized), and N-methylated carboxylic acid metabolites. Mean plasma levels of dexmedetomidine, total radioactivity, G-DEX-1, G-DEX-2, H-1, and H-3 are shown in figure 3. Table 1 shows the plasma distribution of dexmedetomidine and metabolites. As can be seen in table 1, the majority of the total AUC_{0-24} radioactivity was comprised by dexmedetomidine (14.7%), G-DEX-1 and G-DEX-2 (42%), glucuronide of N-methylated hydroxy metabolite (21%), and H-3, an uncharacterized metabolite (10.5%). G-OH, COOH, N-methyl, and H-2 occur in small quantities ranging from 0.3% to 3.0%. About 6% remains unknown. Table 2 shows the pharmacokinetic parameters of dexmedetomidine and metabolites. The terminal half-lives of dexmedetomidine and most of the metabolites are under five hours (associated radioactivity was not detectable) except for H-1, H-2, H-3, and the unknown fraction.

The majority of radioactivity was excreted into the urine. After nine days, an average of 95% was recovered in the urine with only 4% in the feces. Most of the radioactivity was rapidly excreted since about 85% of the radioactivity recovered in the urine was excreted within 24 hours after the infusion. No unchanged dexmedetomidine was found in the urine or feces.

Table 3 shows the fractionated cumulative urinary excretion profile of [^{3}H]Dexmedetomidine. N-glucuronide metabolites of dexmedetomidine, G-DEX-1 and G-DEX-2, accounted for about 34% of its cumulative urinary excretion. In addition, metabolites formed by aliphatic hydroxylation of parent drug (OH, G-OH, and COOH together) represented about 14% of the dose in urine. The N-Methyl metabolite itself was a minor circulating component and was undetected in urine. However, the N-methyl metabolite can further be carboxylated and/or undergo glucuronidation. Together, the N-methylation pathway accounted for about 18% of the [^{3}H]dexmedetomidine dose in urine. Approximately, 28% of the urinary metabolites have not been identified.

Table 4 shows the fractionated cumulative fecal excretion profile. COOH, OH, G-DEX-1, G-DEX-2, H-1, and dexmedetomidine appear in low quantities. A large fraction still remains uncharacterized. However, the total fecal excretion comprises only about 3.5% of the total dose.

Figure 2. Mean plasma radioactivity profile following a ten minute infusion of 2 µg/kg [^{3}H]dexmedetomidine.

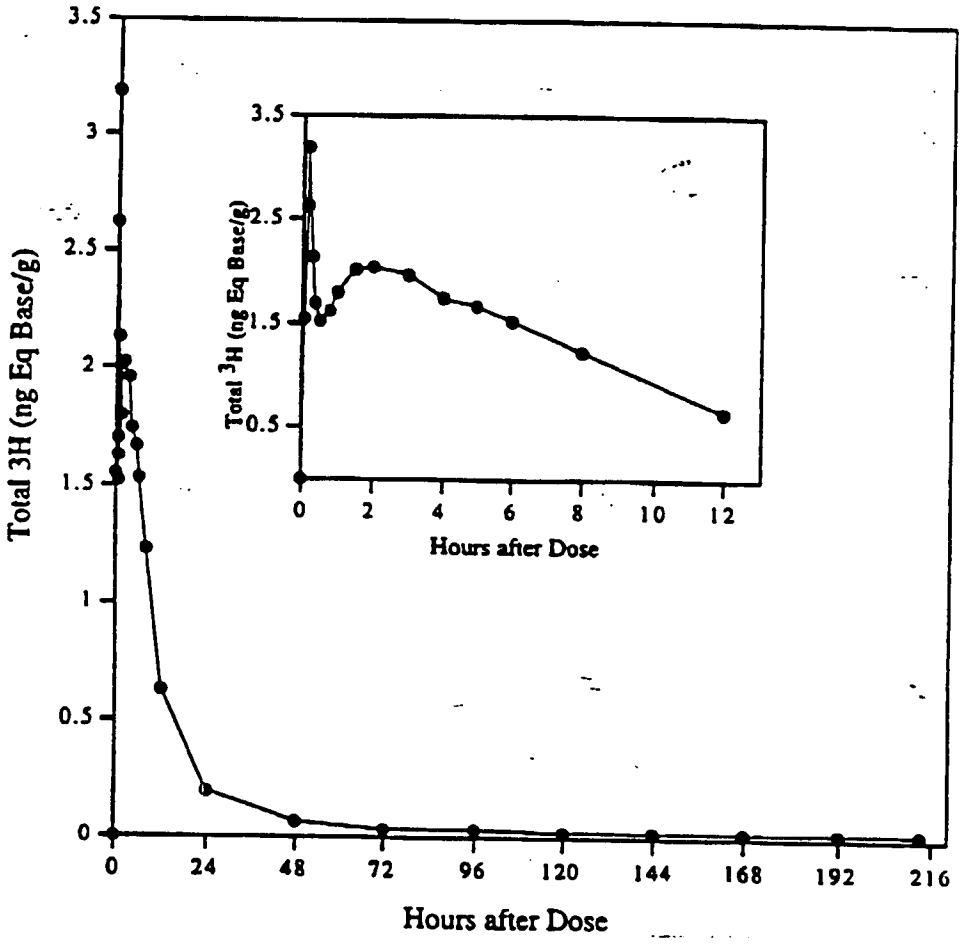


Figure 3. Mean plasma levels of total radioactivity, dexmedetomidine and metabolites following a ten minute infusion of 2 μg/kg [^{3}H]dexmedetomidine.

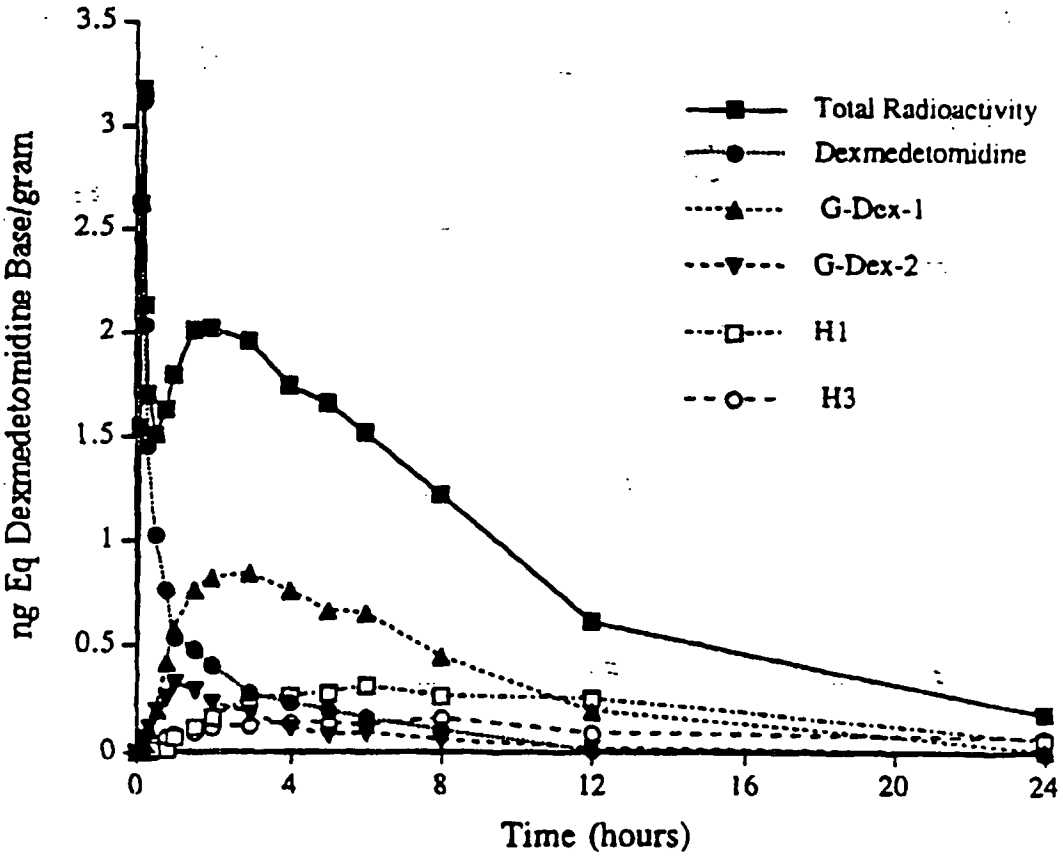


Table 1. Plasma distribution of dexmedetomidine and metabolites following a ten minute infusion of 2 μg/kg [^{3}H]dexmedetomidine.

Plasma Component	AUC_{0-24} (ng Eq·h/g)	% AUC_{0-24} Total Radioactivity
Dexmedetomidine	3.26	14.70
G-Dex-1	7.80	35.19
G-Dex-2	1.37	6.17
G-OH	0.67	3.02
COOH	0.24	1.10
N-Methyl	0.06	0.29
H-1	4.56	20.55
H-2	0.54	2.42
H-3	2.32	10.45
H-4	0.07	0.33
Others	1.28	5.78
Total ^{3}H	22.17	100.00

G-Dex-1 and G-Dex-2 = N-glucuronides of parent drug
G-OH = glucuronide of the hydroxy metabolite
COOH = carboxylic acid metabolite (MPV-1306)
H-1 = glucuronide of the N-methylated hydroxy metabolite
H-2, H-3 = uncharacterized metabolites
H-4 = N-methylated carboxylic acid metabolite
N-Methyl = N-methyl metabolite (MPV-1709)

Table 2. Pharmacokinetic parameters of dexmedetomidine and metabolites following a ten minute infusion of 2 μg/kg [^{3}H]dexmedetomidine.

	Mean ± SD						
Metabolite	C_{max} (ng Eq/g)	T_{max} (h)	$t_{1/2}$* (h)	$AUC_{0-\infty}$ (ng Eq·h/g)	CL (L/h)	V_{ss} (L)	V_β (L)
Dex	3.12 ± 0.27 (n = 5)	0.16 ± 0.02 (n = 5)	2.85 ± 1.10 (n = 3)	3.49 ± 0.68 (n = 3)	42.6 ± 7.1 (n = 3)	143.9 ± 15.5 (n = 3)	182.1 ± 36.0 (n = 3)
G-Dex-1	0.94 ± 0.18 (n = 5)	3.10 ± 1.75 (n = 5)	3.60 ± 0.09 (n = 4)	8.35 ± 1.52 (n = 4)	3.70 ± 0.3 (n = 4)		19.1 ± 1.7) (n = 4)
G-Dex-2	0.34 ± 0.10 (n = 5)	1.15 ± 0.34 (n = 5)	2.76 ± 0.89 (n = 3)	1.61 ± 0.35 (n = 3)	14.2 ± 2.1 (n = 3)		58.9 ± 13.0 (n = 3)
G-OH	0.12 ± 0.03 (n = 5)	1.60 ± 0.42 (n = 5)	4.86 (n = 1)	0.64 (n = 1)	15.9 (n = 1)		111.5 (n = 1)
COOH	0.04 ± 0.03 (n = 5)	7.80 ± 9.39 (n = 5)					
H-1	0.34 ± 0.04 (n = 5)	7.40 ± 3.29 (n = 5)	5.64 ± 0.95 (n = 5)	4.91 ± 0.70 (n = 5)	0.0 ± 0.5 (n = 5)		37.1 ± 3.8 (n = 5)
H-2	0.07 ± 0.01 (n = 5)	4.95 ± 2.65 (n = 5)	7.48 (n = 1)	0.85 (n = 1)	0 (n = 1)		0 (n = 1)
H-3	0.17 ± 0.06 (n = 5)	1.50 ± 2.03 (n = 5)	14.02 (n = 1)	4.25 (n = 1)	0 (n = 1)		0 (n = 1)
Others[a]	0.20 ± 0.03 (n = 5)	4.10 ± 1.52 (n = 5)	8.34 (n = 1)	1.66 (n = 1)	19.(0) (n = 1)		236.2 (n = 1)

* Presented as the harmonic mean. If the time span used to calculate $t_{1/2}$ was less than $t_{1/2}$, the half life and pharmacokinetic parameters calculated from $t_{1/2}$ were not included in summary statistics.

[a] Includes the N-methyl and H-4 metabolites

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Table 3. Urinary distribution of dexmedetomidine and metabolites following a ten minute infusion of 2 µg/kg [^{3}H]dexmedetomidine.

Metabolite	Urine Sample(h)/% ^{3}H-Dose					Mean	SD
	H101	H102	H103	H104	H105		
Dexmedetomidine	nd	nd	nd	nd	nd	0.00	0.00
G-Dex1	16.10	24.00	21.07	19.04	17.57	19.56	3.09
G-Dex2	13.66	18.25	14.72	14.19	14.36	14.43	2.49
OH	1.35	0.67	1.36	1.05	1.11	1.11	0.28
G-OH	8.35	8.15	6.88	7.11	7.79	7.66	0.64
COOH	6.01	3.60	4.02	5.17	5.20	4.80	0.98
H-1	16.36	14.86	12.43	15.27	13.61	14.51	1.52
H-4	4.56	3.08	3.11	3.94	4.10	3.76	0.65
Others	29.53	20.42	28.02	28.53	33.58	28.02	4.77
% Dose Excreted	95.92	93.03	91.61	94.30	94.31	93.83	1.61

G-Dex1 and G-Dex2 = N-glucuronide conjugates of parent drug
COOH = carboxylic acid metabolite (MPV-1306)
OH = hydroxylated metabolite (MPV-1305)
G-OH = glucuronide conjugate of the hydroxy metabolite
H-1 = N-methylated glucuronide conjugate of the hydroxy metabolite
H-4 = N-methylated carboxylic acid metabolite
nd = not detected

Table 4. Fecal distribution of dexmedetomidine and metabolites following a ten minute infusion of 2 μg/kg [^{3}H]dexmedetomidine.

Metabolite	Fecal Sample % ^{3}H-Dose*					Mean	SD
	H101 59 & 77 h	H102 25 & 28 h	H103 24 & 99 h	H104 57 & 72 h	H105 57 & 78 h		
Dexmedetomidine	nd	0.10	0.14	nd	0.07	0.06	0.06
COOH	0.50	0.38	0.36	0.61	0.52	0.47	0.10
OH	0.17	0.29	0.44	0.02	nd	0.18	0.19
G-OH	nd	0.01	nd	0.11	nd	0.04	0.06
G-Dex1	nd	0.20	0.17	nd	0.06	0.09	0.10
G-Dex2	nd	0.03	nd	nd	nd	0.01	0.01
H-1	0.17	0.26	0.22	0.08	0.25	0.19	0.07
H-3	0.04	0.06	0.08	0.02	0.00	0.04	0.03
Others	2.45	2.12	2.81	1.69	2.39	2.29	0.42
% Dose Excreted	3.32	3.54	4.22	2.53	3.29	3.38	0.61

G-Dex1 and G-Dex2 = N-glucuronide conjugates of parent drug
COOH = carboxylic acid metabolite (MPV-1306)
OH = hydroxylated metabolite (MPV-1305)
G-OH = glucuronide conjugate of the hydroxy metabolite
H-1 = N-methylated glucuronide conjugate of the hydroxy metabolite
H-3 = uncharacterized metabolite
nd = not detected
* Total percent of dose excreted for each individual at timepoints listed

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HEPATIC IMPAIRMENT

Study Type: Hepatic Impairment.

Protocol Title: A Phase I, open label study to evaluate the safety and pharmacokinetics of dexmedetomidine in subjects with impaired hepatic function.

NDA: 21-038 **Submission Date:** 12/18/98 **Volume:** 1.50 **Protocol:** DEX-95-009

Clinical Investigators: The principal investigators were Dr. Baughman at University of Illinois Hospital, Chicago, Illinois and Dr. Stuart Harris at Seaview Research, Miami, Florida.

Analytical Investigator: Oneida Research Services, Inc., Whitesboro, New York

Single Dose: Yes **Parallel Group**: Yes **Other Design**: Phase I, Two-Centre, Open-Label.

Subjects: A total of forty subjects, 22 males and 18 females, between the ages of 32 and 62 years were enrolled in the study. Subjects with hepatic impairment were categorized using the Child-Pugh classification based on five measurements (ascites, encephalopathy, bilirubin, albumin and prothrombin time). Two subjects (Subjects 103 and 111) appeared not to have received dexmedetomidine and one subject (Subject 110) appeared to have only received a fraction of the dexmedetomidine dose. These three subjects were not included in the pharmacokinetic analyses in this report. A summary (mean ± SD) of the demographic information is provided in the following table:

Hepatic Function	N	Age (yr)	Height (cm)	Weight (kg)
Normal Healthy	18	46.1 ± 8.6	169.8 ± 8.5	78.6 ± 13.2
Mildly Impaired	6	45.0 ± 8.7	170.6 ± 13.50	72.6 ± 17.8
Moderately Impaired	7	45.1 ± 8.6	166.6 ± 6.9	76.4 ± 23.0
Severely Impaired	6	50.2 ± 6.1	175.3 ± 11.5	89.1 ± 10.1

Formulation

Treatment Group	Dose	Dosage Form	Strength	Lot
Control Group Mildly Impaired Moderately Impaired Severely Impaired	0.6 µg/kg	Sterile solution	200 µg/mL	14094VH and 16104VH

Analytical Methodology

[redacted]

[redacted]

Labeling Claims:
In subjects with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C), clearance values were lower than in healthy subjects. The mean clearance values for subjects with mild, moderate, and severe hepatic impairment were 74%, 64% and 53%, of those observed in the normal healthy subjects, respectively. Mean clearances for free drug were 59%, 51%, and 32% of those observed in the normal healthy subjects, respectively.

Although [redacted] is dosed to effect, it may be necessary to consider dose reduction depending on the degree of hepatic impairment.

Objective: The objective of the study was to evaluate the effect of various degrees of hepatic impairment on the safety and pharmacokinetics of dexmedetomidine in humans. This report compares the pharmacokinetics of dexmedetomidine in a group of normal healthy subjects to those from subjects with mild, moderate or severe hepatic impairment.

Study Design: This was a Phase 1, two-center, open-label, single-period, single-dose study in which normal healthy subjects and subjects with mild, moderate and severe hepatic impairment received an intravenous infusion of 0.6 μg/kg of dexmedetomidine hydrochloride over ten minutes.

Results:

The mean ± standard deviation of dexmedetomidine pharmacokinetic parameters obtained in the normal healthy subjects and subjects with various degrees of hepatic impairment are summarized in table 1.

Following a 10-minute infusion of dexmedetomidine at 0.6 μg/kg, mean dexmedetomidine CL values were lower in subjects with hepatic impairment than in healthy subjects, which is consistent with the knowledge that dexmedetomidine is eliminated primarily by hepatic metabolism and is highly bound to plasma proteins. As a result of reduced serum albumin, the fraction of dexmedetomidine that was bound to plasma proteins decreased statistically significantly in subjects with hepatic impairment compared to healthy subjects. The mean CL values for subjects with mild, moderate, and severe hepatic impairment were only 74%, 64% and 53%, respectively, of those observed in the normal healthy subjects. Compared to the subjects with normal hepatic function (mean $t_{1/2}$ of 2.5 hours), the mean $t_{1/2}$ for the subjects with mild, moderate or severe hepatic impairment were prolonged to 3.9 hours, 5.4 and 7.4 hours, respectively. Therefore, the dose of dexmedetomidine may need to be reduced in subjects with hepatic impairment depending on the degree of impairment. Metabolite pharmacokinetic data was not available from this study.

Table 1. The mean ± standard deviation of dexmedetomidine pharmacokinetic parameters obtained in the normal healthy subjects and subjects with various degrees of hepatic impairment.

Parameter (Units)	Normal Healthy Subjects (N = 18)	Mild Hepatic Impairment (N = 6)	Moderate Hepatic Impairment (N = 7)	Severe Hepatic Impairment (N = 6)
Dose (μg)	39.9 ± 6.7	36.9 ± 9.0	38.8 ± 11.7	45.2 ± 5.1
Fraction Bound (%)*†	89.7 ± 1.6	87.9 ± 0.9	86.5 ± 2.0	82.1 ± 3.8
T_{max} (min)	11.7 ± 3.1	10.3 ± 5.1	10.9 ± 2.3	10.3 ± 0.8
C_{max} (ng/mL)	0.901 ± 0.487	0.930 ± 0.319	0.877 ± 0.498	0.760 ± 0.244
$C_{max,f}$ (ng/mL)†	0.103 ± 0.016	0.120 ± 0.025	0.123 ± 0.090	0.136 ± 0.027
$t_{1/2}$ (h)*	2.5 ± 0.5	3.9 ± 1.7	5.4 ± 2.2	7.4 ± 1.4
$t_{1/2}$ (h)‡	2.4 ± 0.5	3.3 ± 1.6	4.6 ± 2.2	7.2 ± 1.8
MRT (h)*	2.9 ± 0.6	3.8 ± 1.9	4.2 ± 1.6	9.5 ± 2.5
CL (L/h)*	41.9 ± 12.7	31.0 ± 11.4	27.0 ± 12.8	22.4 ± 2.4
CLf (L/h)†*	417.7 ± 160.5	247.9 ± 85.5	211.7 ± 140.6	132.9 ±34.6
CL (L/h/kg)	0.54 ± 0.18	0.44 ± 0.17	0.34 ± 0.18	0.25 ± 0.03
V_{ss} (L)	119.6 ± 41.1	102.0 ± 17.5	103.4 ± 35.3	209.2 ± 40.0
$V_{ss,f}$ (L)†*	1238.7 ± 488.6	776.0 ± 172.1	741.0 ± 338.3	1166.9 ± 217.1
V_{ss} (L/kg)	1.54 ± 0.55	1.49 ± 0.44	1.31 ± 0.49	2.36 ± 0.49

‡ Harmonic mean and pseudo standard deviation. * Statistical significant hepatic effects ($p < 0.05$)

† Corresponding pharmacokinetic parameters for free dexmedetomidine resulted in N=12, 3, 6, and 5 for the normal healthy subjects and the subjects with mild, moderate and severe hepatic impairment, respectively. This was due to the limited sample volume for protein binding analysis.

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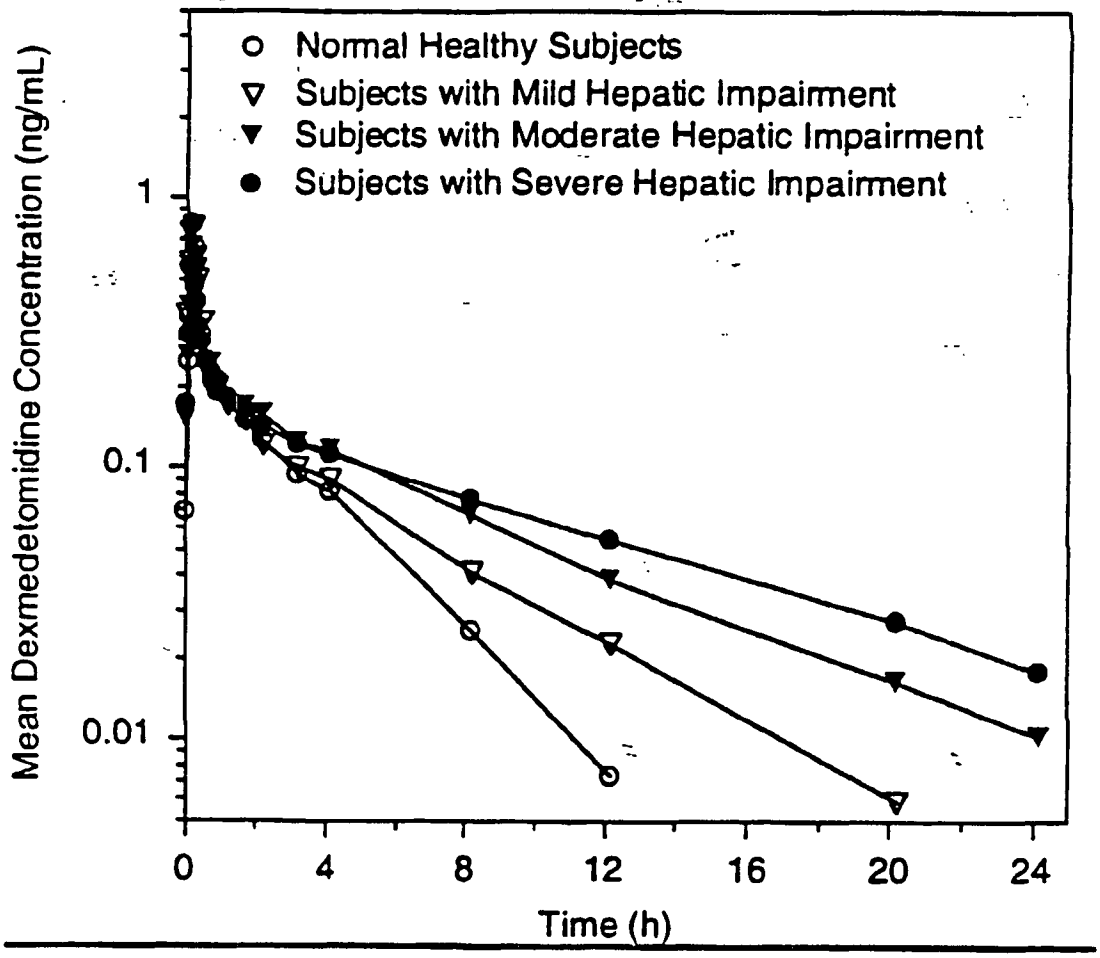
Figure 1. Mean dexmedetomidine plasma concentration versus time profiles following a 10-minute I.V. infusion of dexmedetomidine.



RENAL IMPAIRMENT

Study Type: Renal Impairment

Protocol Title: A Phase 1, single-center, open-label study to assess the safety and pharmacokinetics of dexmedetomidine in normal subjects and subjects with severe renal impairment (Protocol DEX-95-008)

NDA: 21-038 **Submission Date:** 12/18/98 **Volume:** 1.49 **Protocol:** DEX-95-008

Clinical Investigators: The principal investigators were Dr. Robert Fragen at Northwestern University Medical School, Chicago, Illinois and Dr. Ned Kelley at Pharmaceutical Product Development, Clinical Research Unit (PPD-CRU), Morrisville, North Carolina.

Analytical Investigator: Oneida Research Services, Inc., Whitesboro, New York

Single Dose: Yes **Parallel Group**: Yes **Other Design**: Phase I, Single-Centre, Open-Label.

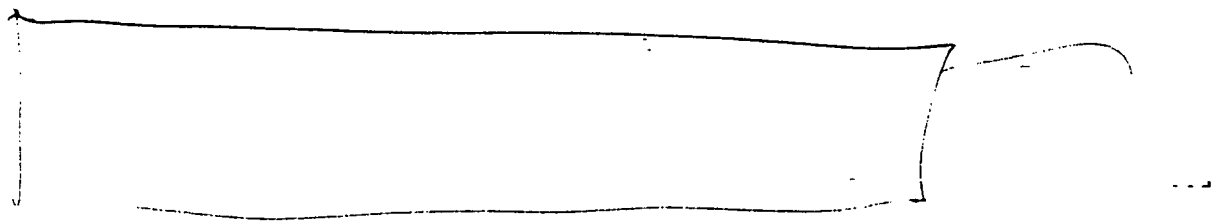
Subject Breakdown

Demographics	Control Group	Severe Renal Impairment Group
Number	6	6
Age (mean (range))	49.0 (33-62)	48.3 (32-60)
Weight (mean (range))	92.6 (47-127)	95.7 (51-119)

Formulation

Treatment Group	Dose	Dosage Form	Strength	Lot
Control Group Severe Renal Impairment group	0.6 µg/kg	Sterile solution	200 µg/mL	11071 VH and 17123VH

Analytical Methodology



Labeling Claims

[redacted] pharmacokinetics (C_{max}, T_{max}, AUC, $t_{1/2}$, CL, and V_{SS}) were not different in subjects with severe renal impairment (Cr Cl: <30 mL/min) compared to healthy subjects.

Objective: The objective of the study was to evaluate in subjects the effect of severe renal impairment on the pharmacokinetics of dexmedetomidine. This report compares the pharmacokinetics of dexmedetomidine in a group of normal healthy subjects to those from a group of subjects with severe renal impairment.

Study Design: This was a Phase 1, two-center, open-label, single-period, single dose study in which six normal healthy subjects and six subjects with severe renal impairment received an intravenous infusion of 0.6 µg/kg of dexmedetomidine-HCl over ten minutes using a computer controlled infusion pump.

Pharmacokinetic Results:

Figure 1 shows the plasma concentration time profile of dexmedetomidine in healthy control subjects and patients with severe renal impairment. The profiles are remarkably similar in both groups. The mean ± standard deviation of dexmedetomidine pharmacokinetic parameters obtained in normal healthy subjects and subjects with severe renal impairment are summarized in the following table.

Parameter	Normal Subjects	Severe Renal Impairment Subjects
C_{max} (ng/mL)	0.960 ± 0.432	0.833 ± 0.258
$t_{1/2}$ (hour)*	2.28 ± 0.39	2.05 ± 0.30
MRT (hour)	2.81 ± 0.25	2.58 ± 0.44
CL (liter/hour)	41.2 ± 6.2	50.0 ± 18.8
CL (liter/hour/kg)	0.470 ± 0.108	0.560 ± 0.246
Vss (liter)	117.1 ± 26.9	127.2 ± 44.9
Vss, (liter/kg)	1.31 ± 0.26	1.40 ± 0.52

* The harmonic mean and pseudo-standard deviation were calculated to be 2.22 ± 0.39 hours and 2.02 ± 0.25 hours for the normal subjects and the subjects with severe renal impairment, respectively.

There were no statistically significant differences in the dexmedetomidine pharmacokinetics between the normal healthy subjects and subjects with severe renal impairment. In addition, no significant associations were observed between dexmedetomidine clearance and creatinine clearance values (see figure 2). Metabolite pharmacokinetic data was not available from this study.

Conclusions: Dexmedetomidine pharmacokinetics were not different in subjects with severe renal impairment compared to normal healthy subjects. Accordingly, for a given administration regimen the pharmacokinetic profile of dexmedetomidine is expected to be independent of the patient's renal function.

Figure 1. Mean dexmedetomidine plasma concentration versus time profiles following a 10-minute intravenous infusion of dexmedetomidine.

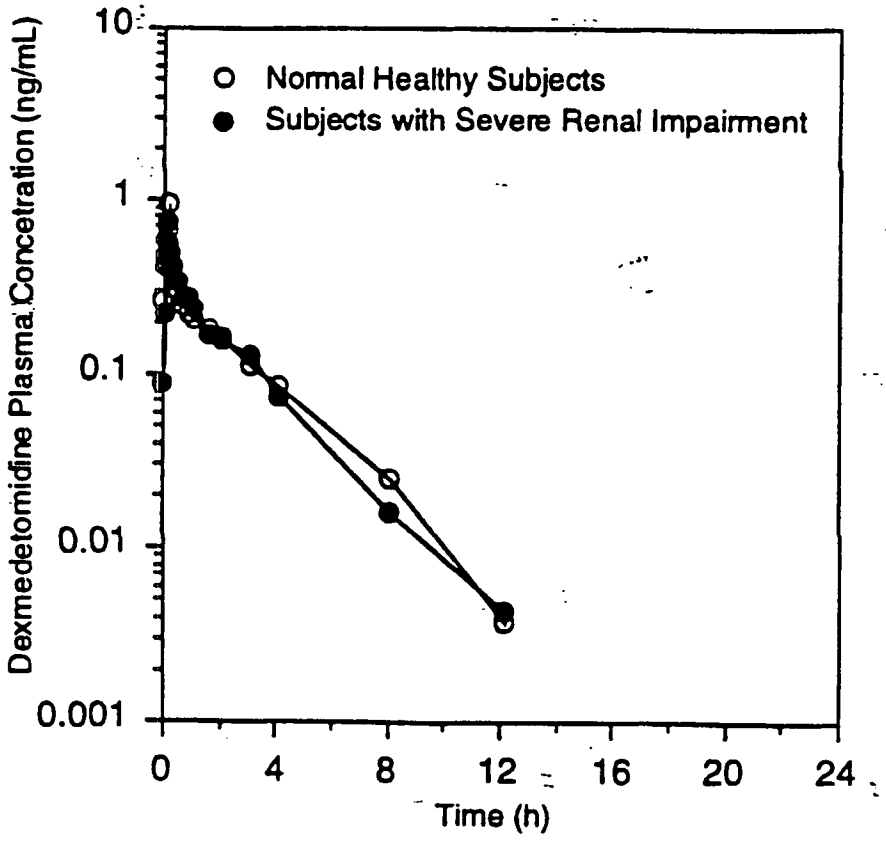


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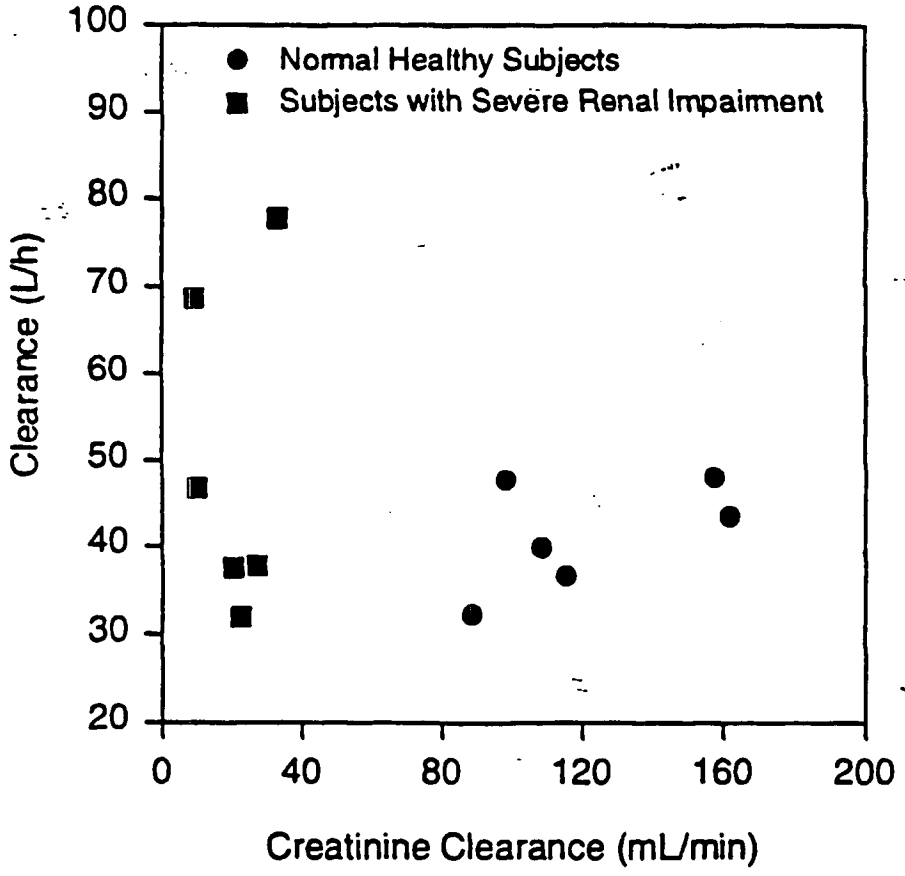
Figure 2. Total clearance versus creatinine clearance for individual subjects.



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EFFECT OF AGE AND GENDER

Study Type: Effect of Age.

Title: A Phase 1, Single Center, Open Label, Parallel Study to Evaluate the Influence of Age on the Pharmacokinetics of Dexmedetomidine in Healthy Volunteers (Protocol DEX-96-013)

NDA: 21-038 Submission Date: 12/18/98 Volume: 1.55 Protocol: DEX-96-013
Clinical Investigator: Elizabeth Youngs, MD, VA Palo Alto Health Care System, CA
Analytical Investigator: Oneida Research Services, Inc., Whitesboro, New York

Single Dose: Yes Parallel Group: Yes Other Design: Phase I, Single-Centre, Open-Label.

Subject Breakdown

Demographics	18-40 years	41-65 years	Over 65 years
Number (male, female)	9, 11	14, 6	12, 8
Age (mean (range))	31 (21-39)	50 (41-65)	72 (66-83)
Weight (mean (range))	73 (52-117)	82 (50-109)	72 (45-93)

Formulation

Treatment Group	Dose	Dosage Form	Strength	Lot
18 to 40 years 41 to 65 years Older than 65 years	0.6 µg/kg	Sterile solution	200 µg/mL	149094VH

Analytical Methodology

[redacted]

Labeling Claims
Gender:
No difference in [redacted] pharmacokinetics due to gender was observed.
Geriatrics:
The pharmacokinetic profile of [redacted] was not altered by age.

Objective: The objective of the study was to evaluate the pharmacokinetics of dexmedetomidine when administered intravenously as a single 10 minute infusion of 0.6 μg/kg in young, middle aged, and elderly subjects. Included in the design was the goal of enrolling an approximately equal number of male and female subjects. This report addresses the pharmacokinetics of dexmedetomidine observed in the three different age groups with consideration of gender and other demographic descriptors.

Study Design: This was a Phase 1, single-center, open label, parallel study stratified by three age groups; 18 to 40 years, 41 to 65 years, and older than 65, with enrollment of approximately equal numbers of male and female subjects. Each subject received a single 10 minute intravenous infusion of 0.6 μg/kg dexmedetomidine-HCl.

Results: Sixty (60) adult male and female subjects from three different age groups were enrolled. The three age groups were defined as follows: 18-40 years (young), 41-65 years (middle) and older than 65 (elderly). The mean age of the subjects from each group was 31.2, 49.7, and 71.8 years for the young, middle, and elderly groups, respectively.

Mean ± standard deviation of the pharmacokinetic parameter values obtained as a result of the ten minute infusion of dexmedetomidine are presented in the following table 1.

Conclusions:

Dexmedetomidine pharmacokinetics (CL, C_{max}, T_{max}, V_{ss}, β and AUC) were not different between young, middle-age and elderly adult subjects. The same dexmedetomidine infusion is expected to produce the same dexmedetomidine concentration profile and the elimination characteristics are expected to be the same irrespective of age.

Dexmedetomidine pharmacokinetics (CL, C_{max}, T_{max}, V_{ss}, β, and AUC) were not different between male and female subjects, when differences in body weight were accounted for. The same dexmedetomidine infusion is expected to produce the same dexmedetomidine concentration profile and the elimination characteristics are expected to be the same for men and women.

The average clearance for all subjects was 40.6 liter/hour. Terminal half-life averaged 2.19 hours and the mean V_{ss} was 89.8 liter (1. 19 liter/kg).

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Table 1. Pharmacokinetic parameters of dexmedetomidine as a function of age.

Mean ± SD Noncompartmental Pharmacokinetic Parameter Estimates				
		Age Group		
Parameter	Units	Young 18 - 40 Years	Middle 41 - 65 Years	Elderly Over 65 Years
C_{max}	ng/mL	1.483 ± 0.278	1.615 ± 0.275	1.498 ± 0.290
$t_{1/2}$‡	h	2.11 ± 0.48	2.18 ± 0.34	2.28 ± 0.35
$AUC_{0-\infty}$	ng•h/mL	1.01 ± 0.31	1.04 ± 0.21	0.97 ± 0.21
T_{max}	h	0.148 ± 0.018	0.145 ± 0.015	0.150 ± 0.016
MRT	h	2.43 ± 1.27	2.28 ± 0.42	2.42 ± 0.43
CL	L/h	38.1 ± 8.7	41.2 ± 10.1	38.7 ± 9.1
V_{ss}	L	86.4 ± 25.5	91.0 ± 12.4	92.0 ± 22.0
V_{ss}	L/kg	1.19 ± 0.24	1.13 ± 0.17	1.29 ± 0.23

‡ Presented as the harmonic mean and pseudo-standard deviation.

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DOSE-RANGING

Study Type: Dose-Ranging

Title: A Dose-Ranging Study to Evaluate the Effects of Dexmedetomidine on Sedation.

NDA: 21-038 Submission Date: 12/18/98 Volume: 1.55 Protocol: DEX-97-028

Clinical Investigator: The principal investigators were E.C. Buitenhuis, MD and P.A. Jackson, MD. The study was conducted at U-Gene Research, Bolognalaan 40,3584 CJ, Utrecht, The Netherlands.

Analytical Investigator: Oneida Research Services, Inc., Whitesboro, New York

Subjects:
Seventy-three (73), healthy adult subjects were enrolled at one investigative site. One subject discontinued the study before the entire dose of dexmedetomidine was administered and the results were not used in the summary statistics. Of the 72 subjects (33 males and 39 females) who completed the study, the mean age and weight were 28.5 years (range 18 to 45 years) and 68.6 kg (range 48 to 96 kg), respectively.

Formulation:

Treatment Group	Plasma Target Concentration (ng/mL)	Dosage Form	Strength	Lot
Phase I Part II	0.1, 0.3, 0.45, 0.6, 1.25 0.3, 0.6, 1.25	Sterile solution	100 µg/mL	32-129VH

Analytical Methodology

[redacted]

Labeling Claims: None

Objectives:
The primary objectives of this study were (1) to characterize the dose/response relationship for sedation after single intravenous doses of dexmedetomidine, (2) to select and include 3 doses for the long-term infusion portion of Part II of this study, and (3) to investigate the effects of long-term infusions (12 and 24 hours) of dexmedetomidine on the sedative profile compared to a short term administration.

Study Design: This trial was designed as a two-part, phase 1, placebo-controlled, double-blinded trial.

Part I:
Part I consisted of a dose-ranging study in 40 subjects, 8 subjects per dose (6 active, 2 placebo) to evaluate 5 doses of dexmedetomidine in a sequential fashion starting with the lowest dose. Plasma samples for pharmacokinetic evaluation, sedation scores, hemodynamic and safety assessments were obtained. Upon successful completion of one dose level, the study proceeded to the next level. This rising dose procedure was followed until all 5 doses of dexmedetomidine were studied. Safety was assessed at each dose before proceeding to the next dose. Upon completion of Part I of the study, the three regimens selected for Part II of the study were targeted at concentrations of 0.3 ng/mL, 0.6 ng/mL and 1.25 ng/mL.

Part II:
Part II consisted of four long-term infusion dosing sessions with 32 subjects, 8 subjects per session (6 active, 2 placebo), randomly assigned to each treatment group. Safety was assessed before proceeding to the next dose. In the first dosing session, subjects were assigned to receive a 12-hour infusion of dexmedetomidine targeting 0.3 ng/mL. The remaining sequential dosing sessions were 24-hour infusions targeting 0.3 ng/mL, 0.6 ng/mL and 1.25 ng/mL. Subjects were confined for approximately 3 days in each dosing session. Plasma samples for pharmacokinetic evaluation, sedation scores, hemodynamic and safety assessments were obtained.

Pharmacodynamic Scoring: Ramsay and VAS/Sedation (VAS/S) assessments followed the same schedule as blood pressure and heart rate. Ramsay Sedation Score was evaluated by trained, blinded raters.

VAS/S was a self-administered assessment of the level of sedation. The VAS/S is a 100 mm line with endpoints of "very alert" and "very sleepy." If the subject was too sedated to perform the assessment, and could not be aroused by verbal stimulation, a score of 100 mm was assigned at the study site and this information was noted and transcribed onto the appropriate CRF pages.

Note: According to the reviewing Medical Officer, Dr. Charles Cortinovis, Ramsey scores assessment is a more reliable endpoint than VAS/S assessment.

Results and Discussion

Figures 1 and 2 present the mean dexmedetomidine vs. time profile and mean AUC vs. mean dose profile following 1 hour and 24 hour dexmedetomidine infusions, respectively. The

mean dexmedetomidine pharmacokinetic parameters from parts I and II of the study are presented in Tables 1 and 2. In general, the pharmacokinetic parameter values were similar to those values obtained in previous studies. There were no statistically significant differences in clearance or half-lives across the different regimens. It could be seen from figure 2 and table 2 that there is approximate dose-proportionality in the dexmedetomidine therapeutic concentration range when continuously infused for up to 24 hours. The mean AUC versus mean dose plot showed linearity. The average pseudo-steady-state concentrations approximately doubled and the clearance was similar.

Figure 3 shows the mean Ramsay sedation scores vs. dexmedetomidine concentrations plot. Visual inspection of Ramsay sedation plots indicated that the midrange of sedation (Ramsay score of 3.5) was achievable by dexmedetomidine concentrations in the range of 0.3 ng/mL to 0.6 ng/mL and the maximum Ramsay sedation score achieved in the current study appears to be in the range of about 4.5 to 5. Eight individuals achieved a Ramsay score of 6 on at least one assessment.

Table 1. Mean ± SD pharmacokinetic Parameters, Part I.

Parameter	Loading Infusion Duration (total infusion=1 hour)				
	10 minutes				35 minutes
	Dexmedetomidine Target Concentration (ng/mL)				
	0.1	0.3	0.45	0.6	1.25
Cmax, ng/mL	0.21 ± 0.11	0.83 ± 0.41	0.91 ± 0.29	1.76 ± 0.71	2.40 ± 0.56
$t_{1/2}$*, hour	1.80 ± 0.36	2.08 ± 0.48	2.00 ± 0.09	1.92 ± 0.42	2.20 ± 0.52
CL, liter/hour	41.5 ± 12.9	30.0 ± 4.6	42.9 ± 7.5	33.7 ± 14.1	39.6 ± 10.5
V_{ss}, liter	105.5 ± 42.6	76.2 ± 28.4	88.9 ± 14.5	72.9 ± 31.3	91.5 ± 18.8
C_{et}#, ng/mL	0.08 ± 0.01	0.26 ± 0.04	0.37 ± 0.08	0.62 ± 0.13	1.25 ± 0.33

* Harmonic mean and pseudo standard deviation.
# concentration of dexmedetomidine at the end of infusion.

Table 2. Mean ± SD pharmacokinetic Parameters, Part II.

Parameter	Loading Infusion (min)/Total infusion duration (hrs)			
	10 min/12 hrs	10 min/24hrs	10 min/24 hrs	35 min/24 hrs
	Dexmedetomidine Target Concentration (ng/mL)			
	0.3	0.3	0.6	1.25
C_{max}, ng/mL	0.87 ± 0.25	1.05 ± 0.17	1.59 ± 0.51	2.40 ± 0.59
$t_{1/2}$*, hour	1.78 ± 0.30	2.22 ± 0.59	2.23 ± 0.21	2.50 ± 0.61
CL, liter/hour	46.3 ± 8.3	43.1 ± 6.5	35.3 ± 6.8	36.5 ± 7.5
V_{ss}, liter	88.7 ± 22.9	102.4 ± 20.3	93.6 ± 17.0	99.6 ± 17.8
Avg Css#, ng/mL	0.27 ± 0.05	0.27 ± 0.05	0.67 ± 0.10	1.37 ± 0.20

* Presented as harmonic mean and pseudo standard deviation.
\# Avg Css = Average steady-state concentration of dexmedetomidine. (2.5 - 9 h samples for 12 hour infusion and 2.5 - 18 h samples for 24 hour infusions.).

Table 3. Maintenance infusion rates and corresponding expected steady state plasma dexmedetomidine concentrations.

'Target' Steady State Concentrations (ng/mL)	Maintenance Infusion Rates (µg/kg/hour)
0.3	0.17
0.5	0.28
0.7	0.39
0.9	0.50
1.25	0.70

Figure 1. Mean dexmedetomidine plasma concentration vs. time profiles after the infusion of dexmedetomidine for 1 hour and 24 hours.

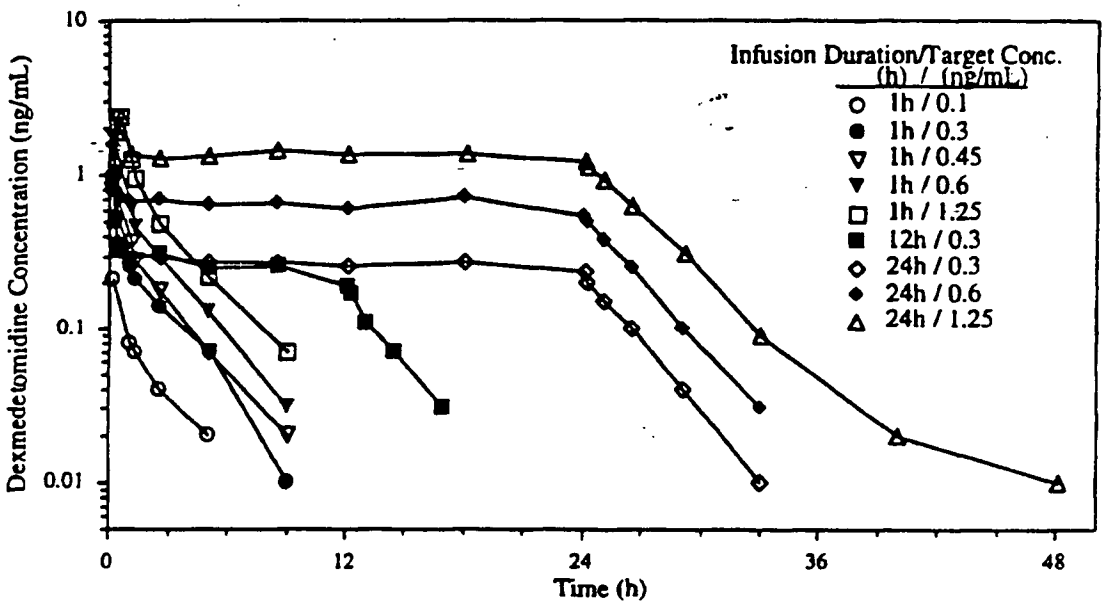

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Figure 2. Dexmedetomidine mean AUC vs. mean dose profile.

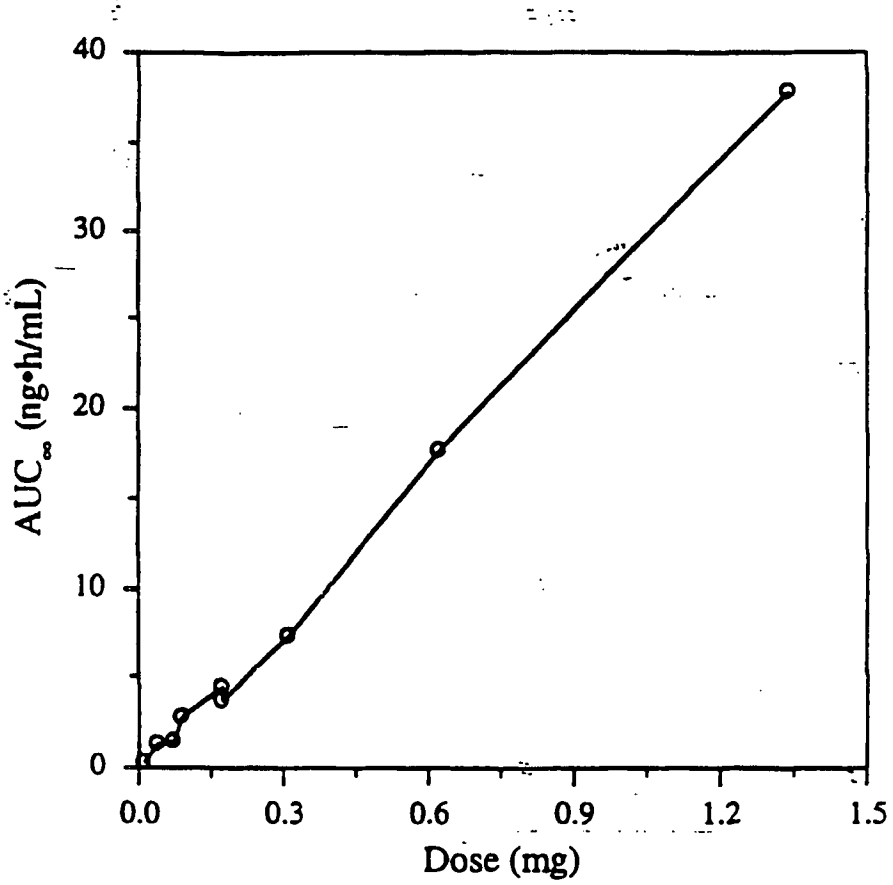

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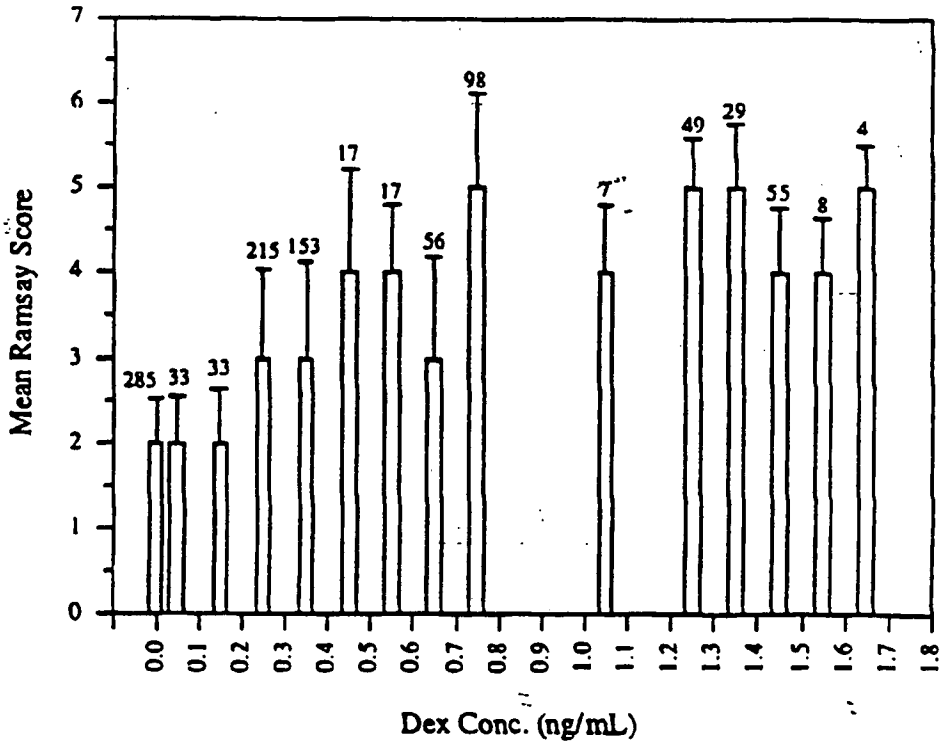
Figure 3. Mean Ramsay sedation scores vs. dexmedetomidine concentrations.



[a] For each Ramsay score, a dexmedetomidine plasma concentration (ng/mL) was linearly interpolated from the surrounding dexmedetomidine values, if not measured. A mean Ramsay score was then calculated for each 0.1 ng/mL increment of dexmedetomidine. Each bar is centered over the mean of the dexmedetomidine increment and represents the mean Ramsay score for that dexmedetomidine concentration range. The number above each bar is the number (N) of Ramsay scores used to compute the mean at that dexmedetomidine concentration range. Bars comprising of less than 4 values were omitted.

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DEXMEDETOMIDINE-ALFENTANIL INTERACTION

Study Type: Drug-Drug Interactions.

Title: Pharmacodynamic Interactions of Dexmedetomidine and Alfentanil in Healthy Volunteers.

NDA: 21-038 **Submission Date**: 12/18/98 **Volume**: 1.53 **Protocol**: DEX-95-011

Clinical Investigator: Ned Kelly, MD, Pharmaceutical Product Development-Clinical Research Unit, Morrisville, North Carolina.

Analytical Investigator: Oneida Research Services, Inc., Whitesboro, New York

Subject Breakdown

Healthy = yes Number=9 Male=9
Weight *mean* 80 kg *range* 69-85 kgs
Age *mean* 31 years *range* 22-45 years

Formulation

Treatment Group	Dose	Dosage Form	Strength	Lot
Placebo Low high	0 µg/kg 1.4 µg/kg 2.4 µg/kg	Sterile solution	200 µg/mL	110714VH

Analytical Methodology

[redacted]

Labeling Claims

Co-administration of [redacted] is likely to lead to an enhancement of effects with anesthetics, sedatives, hypnotics, and opioids. Specific studies have confirmed these effects with sevoflurane, isoflurane, propofol, alfentanil, and midazolam. No pharmacokinetic interactions between dexmedetomidine and these agents were demonstrated. However, due to pharmacokinetic

effects, when co-administered wi[redacted] a reduction in dosage with these agents may be required.

Objectives

To determine the effects of two concentrations of dexmedetomidine upon ventilatory and analgesic responses to incremental increases in alfentanil concentrations.

Study Design:

This was a single-center, double-blinded, randomized, placebo controlled, three-period crossover, phase I study in which 9 healthy male subjects participated. During a treatment session, the volunteers received intravenous infusions of dexmedetomidine or placebo using a computer controlled infusion pump (CCIP) to target plasma concentrations of 0, 0.3 or 0.6 ng/mL. The CCIP was used to rapidly attain and maintain target plasma concentrations for up to 6.75 hours. Forty five minutes after the infusion of dexmedetomidine or placebo was initiated, alfentanil was infused with a second CCIP, in a manner designed to achieve a stepwise logarithmically ascending alfentanil concentration profile. Each alfentanil step lasted 30 minutes. Sessions were to be separated by a minimum of 14 days. During each step, blood samples for drug concentration were drawn and the psychometric performance tests, ventilatory measurements and pain assessments were conducted.

Results and Discussion

This study was designed with pharmacodynamic assessments as the primary goal. As a result, blood samples for dexmedetomidine assay were available only during the pseudo-steady-state portion of the experiment, precluding the determination of all pharmacokinetic parameters with the exception of steady-state clearance and steady state concentration.

The mean doses of dexmedetomidine were 1.4 µg/kg and 2.4 µg/kg for low and high dose dexmedetomidine regimens, respectively. The average duration of administration was 5.2 hours and 4.4 hours for the low and high dose dexmedetomidine regimens, respectively.

Alfentanil was given for an average duration of 4.5 hours and 3.5 hours for the low and high dose dexmedetomidine regimes, respectively. The mean doses of alfentanil administered were 99.5 µg/kg and 55.1 µg/kg, respectively.

The overall mean dexmedetomidine steady state clearances in the current study was 38.0 liter/hour, a value similar to those obtained in previous studies. Steady state clearances for the two regimens differed with the lower clearance of 33 liters/hour associated with higher pseudo-steady-state mean concentrations of 0.86 ng/mL. The low dose regimen was associated with a higher clearance of 42.8 liters/hour and pseudo-steady-state concentration of 0.358 ng/mL. Average pseudo-steady-state concentrations achieved in the two regimens were greater than the intended or targeted concentrations because the clearance used to drive the CCIP was higher than the clearance estimated in the current study.

Alfentanil AUC estimates, computed from zero through the last step for which data was available in all treatment groups, on a subject-by-subject basis, indicated a 7% greater area as compared to the placebo regimen, irrespective of low or high dexmedetomidine regimen indicating that dexmedetomidine does not significantly influence the pharmacokinetics of alfentanil.

DEXMEDETOMIDINE-MIDAZOLAM INTERACTION

Study Type: Drug-Drug Interactions.

Title: Pharmacokinetics and Pharmacodynamics of Co-Administered Dexmedetomidine and Midazolam.

NDA: 21-038 **Submission Date**: 12/18/98 **Volume**: 1.58 **Protocol**: DEX-95-005

Clinical Investigator: Philip T. Leese, MD, Innovex Inc., Lenexa, Kansas.

Analytical Investigator: Oneida Research Services, Inc., Whitesboro, New York

Single Dose: Yes **Cross Over**: Yes **Other Design**: Phase I, Three-period, Single-Centre, double-blinded, One week washout between each period.

Subject Breakdown

Healthy = yes Number=19 Male=9 Female=10

Age *mean* 30 years *range* 19-45 years

Formulation

Treatment Group	Dose	Dosage Form	Strength	Lot
Placebo 0.2 ng/mL 0.4 ng/mL	0 µg 107.6 µg 205.9 µg	Sterile solution	 200 µg/mL 200 µg/mL	08-046VH (midazolam-7646)

Analytical Methodology

[redacted]

Labeling Claims

Co-administration of [redacted] is likely to lead to an enhancement of effects with anesthetics, sedatives, hypnotics, and opioids. Specific studies have confirmed these effects with sevoflurane, isoflurane, propofol, alfentanil, and midazolam. No pharmacokinetic interactions between dexmedetomidine and these agents were demonstrated. However, due to pharmacokinetic effects, when co-administered wi[redacted] a reduction in dosage with these agents may be required.

Dose Administration

Dexmedetomidine or placebo was administered as a loading infusion given for 10 minutes followed by a maintenance infusion of up to 12 hours. The infusion rates were designed to achieve and maintain a steady-state plasma dexmedetomidine level of 0.2 ng/mL or 0.4 ng/mL. Dexmedetomidine loading infusions were administered at a rate of 1.7 or 3.3 µg/kg/hr and the maintenance infusions were given at a 0.14 or 0.28 µg/kg/hr for the low and high dose dexmedetomidine regimens.

Midazolam was administered stepwise 2 hours after the start of the dexmedetomidine infusion. Each step consisted of two stages, a 5 minute loading infusion followed by a 20 minute maintenance infusion. The following table presents the schedule for the midazolam administration rates (note: the recommended maintenance initial infusion rate is 20 to 200 µg/kg/hr).

Step Number	Loading rate (µg/kg/hr)	Maintenance rate (µg/kg/hr)
1	24.60	4.35
2	21.40	6.52
3	31.0	9.79
4	41.51	14.68
5	67.25	22.02
6	102.74	33.03
7	154.12	49.55
8	222.77	74.32
9	337.30	111.49
10	539.05	167.23
11	744.74	250.84

Results and Discussion

Table 1 shows the pharmacokinetic parameters of dexmedetomidine and midazolam. For dexmedetomidine, it is apparent that the pharmacokinetic parameters were similar at the two dosage regimens. Similarly for midazolam, it is apparent that its pharmacokinetics were similar when coadministered with placebo, 0.2 ng/mL dexmedetomidine target regimen, or 0.4 ng/mL target dexmedetomidine regimen.

Midazolam is metabolized by CYP3A4. The lack of effect of dexmedetomidine on CYP3A4 activity is consistent with dexmedetomidine metabolism. Dexmedetomidine has an IC_{50} value of 0.65 μM towards CYP3A4. A dexmedetomidine concentration of 0.5 ng/mL is approximately equal to 0.0025 μM. Dexmedetomidine concentrations would have to be increased approximately 260 fold to reach the IC_{50}. By design, two different concentrations were targeted for dexmedetomidine-0.2 and 0.4 ng/mL. There were statistically no significant differences noted for midazolam clearance as a function of dexmedetomidine regimen implying a lack of effect of dexmedetomidine on midazolam pharmacokinetics.

Table 1. Mean pharmacokinetic parameters of dexmedetomidine and midazolam.

Noncompartmentally Determined Pharmacokinetic Parameters				
Parameter	Units	Regimens		
		A	B	C
Dexmedetomidine				
C_{max}	ng/mL	0.428	0.822	-
T_{max}	h	1.69	1.26	-
$t_{1/2}$*	h	1.76	1.92	-
MRT	h	2.06	2.34	-
CL	L/h	41.4	39.1	-
C_{EOD}†	ng/mL	0.189	0.426	
V_{ss}	L	83.0	86.8	-
Midazolam				
C_{max}	ng/mL	182.7	130.3	217.4
T_{max}	h	3.58	3.09	3.91
$t_{1/2}$*	h	2.10	2.24	2.21
MRT	h	2.39	2.59	2.89
CL	L/h	32.6	32.1	31.4
V_{ss}	L	76.8	80.4	88.0

Regimen A = 0.2 ng/mL dexmedetomidine target steady state and midazolam administered iv.
Regimen B = 0.4 ng/mL dexmedetomidine target steady state and midazolam administered iv.
Regimen C = Placebo for dexmedetomidine and midazolam administered iv.
† C_{EOD} = concentration just prior to the end of the dexmedetomidine infusion.
* harmonic mean

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DEXMEDETOMIDINE-ISOFLURANE INTERACTION

Study Type: Drug-Drug Interactions.

Title: A Phase I, Single Center, Randomized, Single-Blind, Cross-Over, Controlled Study to Determine the Effects of Dexmedetomidine On Isoflurane Requirements in Healthy Volunteers.

NDA: 21-038 Submission Date: 12/18/98 Volume: 1.54 Protocol: DEX-95-001

Clinical Investigator: Dr. Timothy G.K. Mant, Guy's Drug Research Unit, London.

Analytical Investigator: Oneida Research Services, Inc., Whitesboro, New York

Subject Breakdown
Healthy = yes Number=10 Male=10
Age *mean* 27 years *range* 22-32 years
Formulation

Treatment Group	Target Concentration	Dosage Form	Strength	Lot
Placebo 0.3 ng/mL 0.6 ng/mL	0 µg 0.3 ng/mL 0.6 ng/mL	Sterile solution	200 µg/mL 200 µg/mL	04-118VC

Analytical Methodology

Labeling Claims
Co-administration of ——— is likely to lead to an enhancement of effects with anesthetics, sedatives, hypnotics, and opioids. Specific studies have confirmed these effects with sevoflurane, isoflurane, propofol, alfentanil, and midazolam. No pharmacokinetic interactions between dexmedetomidine and these agents were demonstrated. However, due to pharmacokinetic effects, when co-administered with ——— a reduction in dosage with these agents may be required.

Objectives

To determine the effects of two doses of dexmedetomidine compared to placebo on isoflurane requirements in healthy male volunteers.

Study Design

This was a phase I, single center, randomized, single blind, three-way crossover, controlled study in ten (10) healthy volunteers (study Dex-95-001). Subjects received infusions of placebo or pseudo-steady-state dexmedetomidine target concentrations of 0.3 ng/mL or 0.6 (three stage infusion) ng/mL for two hours prior to receiving isoflurane. The concentration of isoflurane was increased by 0.2% increments, each with a 15 minute equilibration period until the purposeful motor response to an electric nerve stimulus was abolished. Thereafter, the end-tidal isoflurane concentration was decreased by 0.2%, each with a 15 minute equilibration period to identify the concentration at which the motor response reappeared as well as the concentration at which a response to verbal command occurred.

Results and Discussion

There were no statistically significant differences in any of the pharmacokinetic parameters of dexmedetomidine between the two target concentrations of 0.3 ng/mL and 0.6 ng/mL (table 1). This indicates that the pharmacokinetics of dexmedetomidine were unchanged during isoflurane administration. However, based on pharmacodynamic interactions, the sponsor concluded that isoflurane requirements to induce suppression of motor response and response to verbal command are decreased with dexmedetomidine.

Table 1. The main mean ± standard deviation of dexmedetomidine pharmacokinetic parameters obtained after isoflurane administration.

Parameter	0.3 ng/mL Target Concentration	0.6 ng/mL Target Concentration
Css (ng/mL)#	0.352 ± 0.46	0.729 ± 0.106
$t_{1/2}$ (h)*	1.86 ± 0.39	1.94 ± 0.14
C_L (L/h/kg)	0.52 ± 0.06	0.495 ± 0.09
V_{ss} (L/kg)	1.47 ± 0.46	1.33 ± 0.19

* The harmonic mean and pseudo-standard deviation.

average of concentrations measured between 2 hours and end of infusion.

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DEXMEDETOMIDINE-PROPOFOL INTERACTION

Study Type: Drug-Drug Interactions.

Title: A Phase I, Single Center, Randomized, Single-Blind, Cross-Over, Placebo-Controlled Study Evaluating the Effects of Dexmedetomidine On Propofol Requirements in Healthy Volunteers.

NDA: 21-038 **Submission Date**: 12/18/98 **Volume**: 1.52 **Protocol**: DEX-96-019

Clinical Investigator: Dr. Timothy G.K. Mant, Guy's Drug Research Unit, London.

Analytical Investigator: Oneida Research Services, Inc., Whitesboro, New York

Subject Breakdown

Healthy = yes Number=10 Male=10
Age *mean* 24 years *range* 18-28 years

Formulation

Treatment Group	Target Concentration	Dosage Form	Strength	Lot
Placebo 0.5 ng/mL	0 µg 0.5 ng/mL	Sterile solution	100 µg/mL	20150VH

Analytical Methodology

[redacted]

Labeling Claims

Co-administration of [redacted] is likely to lead to an enhancement of effects with anesthetics, sedatives, hypnotics, and opioids. Specific studies have confirmed these effects with sevoflurane,

isoflurane, propofol, alfentanil, and midazolam. No pharmacokinetic interactions between dexmedetomidine and these agents were demonstrated. However, due to pharmacokinetic effects, when co-administered with [redacted], a reduction in dosage with these agents may be required.

Obectives.

To determine the effects of two doses of dexmedetomidine compared to placebo on propofol requirements in healthy male volunteers.

Study Design

This was a phase I, single center, randomized, double blind, two-period crossover, study in ten (10) healthy volunteers. Subjects received infusions of placebo or pseudo-steady-state dexmedetomidine target concentration of 0.5 ng/mL for up to three hours. Forty five minutes after the start of dexmedetomidine infusion, propofol infusion was initiated with a CCIP in a manner designed to achieve a stepwise logarithmically ascending concentration profile. Propofol target concentrations ranged from 1 μg/mL at step 1 to 13.79 μg/mL at step 11. Each propofol step lasted 10 minutes. Propofol and dexmedetomidine infusions were terminated when the subjects were considered to be too sedated .

Results and Discussion

Dexmedetomidine pharmacokinetic parameters in this study after propofol administration were similar to those observed in other studies (table 1). Propofol pharmacokinetics were similar between placebo infusion and dexmedetomidine infusion indicating that dexmedetomidine did not have an effect on propofol pharmacokinetics.

Based on the clinical endpoints, dexmedetomidine was concluded to have a propofol sparing effect i.e., reduced propofol concentrations needed for sedation and anesthesia in the presence of dexmedetomidine.

Table 1. The main mean ± standard deviation of dexmedetomidine and propofol pharmacokinetic parameters.

Parameter	Dexmedetomidine	Propofol	
		Placebo Treatment	Dexmedetomidine Treatment
$t_{1/2}$ (h)*	2.27 ± 0.46	2.33 ± 0.7	2.27 ± 0.82
CL (L/h/kg)	41.5 ± 8.15	119 ± 22.4	124 ± 46.8
V_{ss} (L/kg)	1.71 ± 0.19	3.93 ± 0.82	3.53 ± 1.36

*The harmonic mean and pseudo-standard deviation.

DEXMEDETOMIDINE-ROCURONIUM INTERACTION

Study Type: Drug-Drug Interactions.

Title: Pharmacokinetics and Pharmacodynamics from a Phase I, Single Center, Open-Label Study Assessing the Interaction of Dexmedetomidine and Rocuronium, a Muscle Relaxant, in Healthy Volunteers.

NDA: 21-038 Submission Date: 12/18/98 Volume: 1.54 Protocol: DEX-96-022

Clinical Investigator: Dr. Pekka Talke, University of California, San Francisco.

Analytical Investigator: Oneida Research Services, Inc., Whitesboro, New York

Subject Breakdown

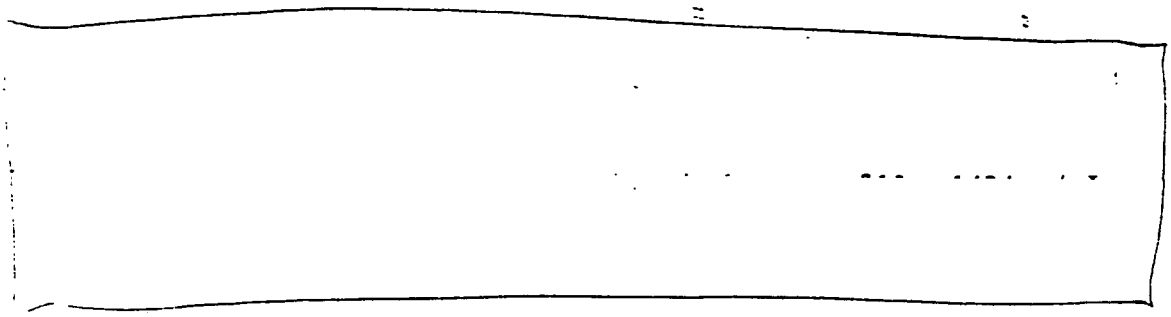
Healthy = yes Number=10 Male=6 Female=4

Age *mean* 31 years *range* 23-43 years

Formulation

Treatment Group	Target Concentration	Dosage Form	Strength	Lot
0.6 ng/mL	0.6 ng/mL	Sterile solution	200 µg/mL	12-081VH

Analytical Methodology



Labeling Claims

No clinically meaningful increases in the magnitude of neuromuscular blockade and no pharmacokinetic interactions were observed with [redacted] and rocuronium administration.

Objectives

To evaluate the effect of dexmedetomidine on the level of rocuronium-induced muscle relaxation in healthy volunteers.