pseudoplasma were superimposable for all plasma and unbound drug in plasma concentrations [A_p^u]. Plots (Fig. 13) of $f/(1-f)$ against m are linear for all [A_p^u] and pass through the origin with slopes of S. The fraction of drug bound to 100% plasma when $m = 1$ can then be calculated (Table III). The human plasma protein binding of etofibrate is 96.89 ± 0.09% (*SD*) for plasma concentrations in the 0.2- to 80-μg/ml range. The human plasma protein binding of clofibrate is 98.23 ± 0.18% (*SD*) for plasma concentrations in the 14- to 108-μg/ml range.

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Pharmacokinetic Model for Diazepam and its Major Metabolite Desmethyldiazepam Following Diazepam Administration

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Abstract □ A five-compartment open model was used to simulate the blood concentration profiles of diazepam and its metabolite, desmethyldiazepam, following single- and multiple-dose administrations of diazepam. The parameter estimates for diazepam were previously reported literature values. The parameter estimates for the metabolite were calculated from literature values of blood concentrations of desmethyldiazepam following the administration of clorazepate. The five-compartment open model suggests that ~50% of the administered diazepam is biotransformed to desmethyldiazepam, and that the elimination profile of the metabolite is not altered by the presence of the drug. The model may also be readily adapted to predict the concentrations of diazepam and desmethyldiazepam in cerebrospinal fluid following the administration of diazepam by simply correcting the blood or plasma concentrations of the drug and metabolite for the degree of plasma protein binding.

Keyphrases □ Diazepam—desmethyldiazepam, pharmacokinetics, single- and multiple-dose administrations, five-compartment open model, blood, CSF □ Desmethyldiazepam—diazepam, pharmacokinetics, single- and multiple-dose administrations, five-compartment open model, blood, CSF □ Pharmacokinetics—diazepam, desmethyldiazepam, single- and multiple-dose administrations, five-compartment open model, blood, CSF

Diazepam (7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one) is effective in the symptomatic relief of tension and anxiety, as well as for the relief of skeletal muscle spasms (1–5). Desmethyldiazepam, the major metabolite of diazepam, is the pharmacologically active metabolite of the prodrugs clorazepate and prazepam, which are also used as anxiolytic agents (6–8).

Diazepam pharmacokinetics have been described previously by a three-compartment model by Kaplan *et al.* (6) and Moolenaar *et al.* (9). Several investigators have described the pharmacokinetic profile of desmethyldiazepam following oral administration of the prodrug clorazepate in terms of a two-compartment open model (8, 10–12). The present report combines the three-compartment open model for diazepam and the two-compartment open model for desmethyldiazepam to define the pharmacokinetic profiles of diazepam and its metabolite following single- and multiple-dose administrations of the drug.

EXPERIMENTAL

Clinical Protocol—The data used in this study were previously reported by Kaplan *et al.* (study A) (6). Briefly, four healthy male volunteers, ages 25–43, each received single 10-mg doses of diazepam administered intravenously and orally 1 week apart. Commencing 1 week thereafter, each subject received a 10-mg oral dose of the drug every 24 hr for 15 days. The subjects were fasted for 7 hr prior to receiving the single-dose administrations, and food was withheld for 1 hr postadministration.

Blood specimens were obtained 1, 2.5, 5, 10, 20, 30, and 45 min and at 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, and 48 hr following intravenous administration, and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, and 48 hr following the single-dose oral administration. Following chronic administration, blood samples were obtained 0 (predose), 0.5, 1, 2, 4, and 24 hr postadministration on day 1; 1, 2, and 24 hr postadministration on days 2–11; 1 and 2 hr postadministration on day 12 and at 0 (predose), 1, 2, 4, 6, 8, 12, 24, 30, 36, 48, 72, 96, 120, 144, 168, 192, and 216 hr postadministration on day 15.

Analytical Method—Blood specimens were analyzed for diazepam and desmethyldiazepam by the electron-capture GLC procedure of de Silva and Puglisi (13), with a sensitivity of 10 and 20 ng/ml, respectively, for each component using a 1-ml specimen.

Pharmacokinetic Model—The five-compartment open model used to describe the pharmacokinetic profiles of diazepam and its major me-

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Table I—Pharmacokinetic Parameters Obtained Following the Single-Dose Administration of 15 mg of Clorazepate Dipotassium to Six Normal Subjects

Parameter	Study B[a]				Study C[b]		Mean ± SD[c]
	1	2	3	4	1	2	
A, ng/ml	177.9	446.7	236.1	962.8	800.8	130.1	459.1 ± 349
α, hr^{-1}	1.13	0.56	1.32	1.42	1.11	0.60	1.02 ± 0.36
B, ng/ml	85.0	79.2	116.7	92.6	65.3	72.4	85.2 ± 181
β, hr^{-1}	0.017	0.010	0.017	0.016	0.013	0.014	0.015 ± 0.003
K_a, hr^{-1}	3.4	0.71	3.6	1.84	1.58	3.43	2.43 ± 1.21
V_{cDD}, l	48.7	58.6	37.3	40.8	33.1	55.3	45.6 ± 10.2
K_{12}, hr^{-1}	0.628	0.287	0.710	0.952	0.819	0.333	0.622 ± 0.265
K_{21}, hr^{-1}	0.480	0.259	0.583	0.430	0.250	0.251	0.376 ± 0.143
K_{Mel}, hr^{-1}	0.041	0.023	0.039	0.054	0.056	0.033	0.041 ± 0.013

[a] Taken from Ref. 7. [b] Taken from Ref. 15. [c] Mean values used as estimates in the pharmacokinetic model.

tabolite, desmethyldiazepam, is presented in Fig. 1. Equations for the blood concentration–time profiles of drug and metabolite were derived by the method of Kaplan *et al.* (14). The pharmacokinetic parameters previously reported in study A were used as the estimates for diazepam (6). Desmethyldiazepam blood concentration–time data following administration of clorazepate, previously reported by Abruzzo *et al.* (study B) (7) and Brooks *et al.* (study C) (15) were fitted using NONLIN (16) to obtain parameter estimates for the metabolite disposition (Table I). The parameters K_{21} and K_{12} in Table I are identical to K_{54} and K_{45} in the present model.

Parameter estimates for K_{14}, the rate of formation of the metabolite following diazepam administration, had not been previously reported in the literature. Initial estimates of K_{14} were obtained based on the fraction (f_m) of diazepam metabolized to desmethyldiazepam calculated both following single-dose and chronic-dose administrations of the drug. To estimate the amount of diazepam biotransformed to desmethyldiazepam following single-dose intravenous and oral administrations, the mean area under the blood concentration–time curve from time 0 to infinity ($AUC_{0\to\infty}$ for desmethyldiazepam in four subjects (Study A) were calculated (Table II). The AUC were determined using the trapezoidal-rule for the blood concentration–time curve from 0 to 48 hr postadministration. The area from 48 hr to infinity was then calculated by dividing the last observed blood concentrations of the metabolite by the overall elimination rate constant (β) for desmethyldiazepam, which was determined following chronic administration of diazepam in the same subjects (6). The mean $AUC_{0\to\infty}$ for desmethyldiazepam following single-dose oral administration of 15 mg of clorazepate (studies B and C), which was used as a standard area representing 10 mg of systemically available metabolite are presented in Table II. The ratio of the desmethyldiazepam $AUC_{0\to\infty}$ for each subject in study A, divided by the mean $AUC_{0\to\infty}$ for the six subjects in studies B and C were used to estimate the fraction (f_m) of diazepam metabolized to desmethyldiazepam in study A. K_{14} is then calculated by multiplying the total elimination rate (K_{TOT}) of the drug by the estimated fraction (f_m) metabolized. K_{TOT} was previously reported as K_{el} in study A (6). K_{14} and the fraction (f_m) of diazepam metabolized to desmethyldiazepam for the four subjects in study A based on the single-dose administration of the drug are reported in Table II.

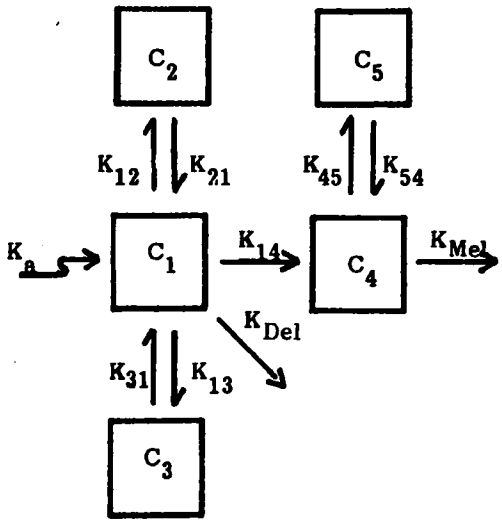

Figure 1—*Five-compartment open pharmacokinetic model used to describe the physiological disposition characteristics of diazepam and its metabolite, desmethyldiazepam.* C_1, C_2, *and* C_3 *are the concentrations of diazepam in the respective compartments;* C_4 *and* C_5 *are the concentrations of desmethyldiazepam in the respective compartments.* K_a *is the first-order absorption rate constant of diazepam;* K_{12}, K_{21}, K_{13}, K_{31}, K_{45}, *and* K_{54} *are the transfer coefficients between compartments;* K_{TOT} *is the total elimination rate of diazepam;* K_{14} *is the rate of metabolism of diazepam to desmethyldiazepam;* K_{Mel} *is the elimination rate of desmethyldiazepam; and* K_{Del} *is the rate of elimination of diazepam via pathways other than metabolism to desmethyldiazepam,* $K_{TOT} = (K_{14} + K_{Del})$.

The pharmacokinetic parameters for diazepam and its metabolite at steady state may also be used to estimate K_{14} and the fraction (f_m) of the drug metabolized to desmethyldiazepam. The differential equations describing the rate of change of desmethyldiazepam concentrations in the central (C_4) and peripheral (C_5) compartments, respectively, following the administration of diazepam based on Fig. 1 may be expressed as:

$$\frac{dC_4}{dt} = C_1K_{14} + K_{54}C_5 - (K_{45} + K_{Mel})C_4 \qquad \text{(Eq. 1)}$$

$$\frac{dC_5}{dt} = C_4K_{45} - C_5K_{54} \qquad \text{(Eq. 2)}$$

At steady state, both dC_4/dt and dC_5/dt equal zero and, based on Eq. 2, C_4K_{45} is equal to C_5K_{54}. Substituting for C_5K_{54} in Eq. 1, C_1K_{14} is then equal to $\overline{C}_4^{ss}K_{Mel}$ at steady state. The conversion of steady-state concentrations of diazepam and desmethyldiazepam to amounts is obtained by multiplying the concentrations by the volume of their respective compartments. Therefore, K_{14} may be expressed as:

$$K_{14} = \frac{\overline{C}_4^{ss} \cdot K_{Mel} \cdot V_{cDD}}{\overline{C}_1^{ss} \cdot V_{cD}} \qquad \text{(Eq. 3)}$$

where V_{cD} and V_{cDD} are the volumes of compartments 1 and 4, and $\overline{C}_4^{ss}$ and $\overline{C}_1^{ss}$ are the steady-state concentrations in compartments 1 and 4 respectively. V_{cD} was previously reported for each subject in study A, and the mean V_{cDD} and K_{Mel} for desmethyldiazepam (Table I) were used in Eq. 3. The average of the mean steady-state blood concentration ($\overline{C}_1^{ss}$) and $\overline{C}_4^{ss}$ from study A (for the drug and metabolite, respectively) following once daily chronic administration of diazepam are reported in Table III. The blood concentrations on days 8–12 and 15 were used to calculate the average of the mean $\overline{C}_1^{ss}$ for diazepam, and blood concentrations on days 11, 12, and 15 were used to determine the average of the mean $\overline{C}_4^{ss}$ for

Table II—Area ($AUC_{0\to\infty}$) Under the Blood Concentration–Time Curves of Desmethyldiazepam Following the Administration of 10 mg of Diazepam [a] or 15 mg of Clorazepate Dipotassium [b] to Normal Subjects

Subject	Studies		f_m[c]	K_{14}[d]
	A	B and C		
1	3864	5014	0.64	0.07
2	3076	7643	0.51	0.12
3	3272	6782	0.55	0.04
4	4015	5720	0.67	0.09
5	—	5350	—	—
6	—	5501	—	—
Mean ±SD		6003 ±1003		

[a] Study A; taken from Ref. 6. [b] Studies B and C; taken from Refs. 7 and 15, respectively. [c] f_m = $AUC_{0\to\infty}$ (study I)/$AUC_{0\to\infty}$ (mean). [d] $K_{14} = K_{TOT}$-f_m; K_{TOT} is reported for each subject in Ref. 6.

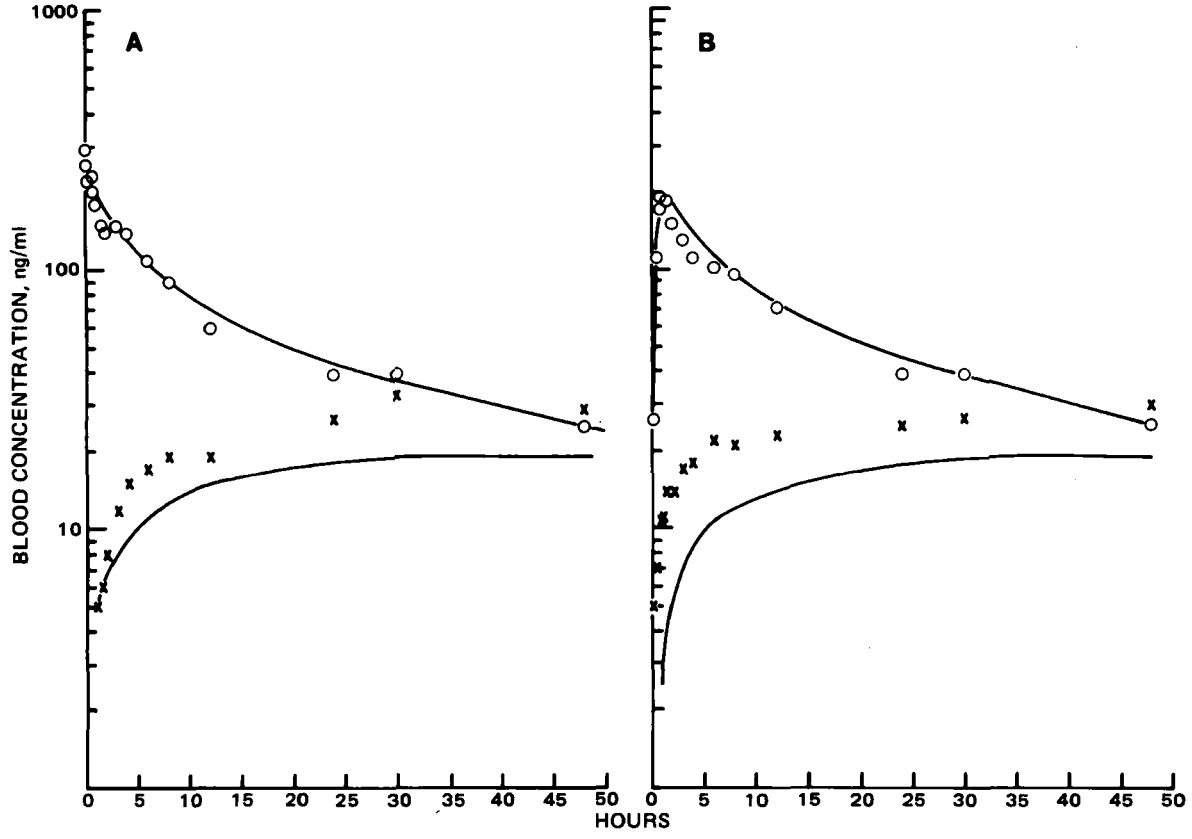

Figure 2—*Blood concentration–time profiles of diazepam (○) and desmethyldiazepam (×) following 10-mg intravenous (A) and oral (B) administrations of diazepam to a normal subject (solid lines represent simulated diazepam and desmethyldiazepam blood concentration–time profiles).*

desmethyldiazepam. The resulting K_{14} values calculated using Eq. 3 are reported in Table III. The fraction (f_m) is then calculated by:

$$f_m = \frac{K_{14}}{K_{TOT}} \qquad \text{(Eq. 4)}$$

where K_{TOT} was previously reported as K_{e1} in study A (6).

The mean K_{14} values from Tables II and III for each subject were used as initial parameter estimates for the pharmacokinetic model in Fig. 1. The blood concentration–time data for diazepam and desmethyldiazepam following single-dose intravenous and oral, and chronic oral administrations were then simulated using the initial parameter estimates previously described.

RESULTS AND DISCUSSION

Model for Blood Concentration–Time Data—The simulated and experimental blood concentration–time profiles of diazepam and desmethyldiazepam following single intravenous and oral doses in one subject are presented in Fig. 2. The corresponding simulated and experimental drug and metabolite blood concentrations following the chronic oral administration of diazepam are presented for the same subject in Fig. 3.

Support for the proposed model required coincidence of simulated and experimental blood concentration–time profiles for diazepam and its metabolite following single-dose intravenous and oral, and chronic oral administrations of the drug to normal subjects. Good agreement was observed between experimental data points and the simulated blood concentration of diazepam in the four subjects from study A. The desmethyldiazepam blood concentrations following chronic dosing were in good agreement with the simulated blood concentrations as shown in Fig. 3B. The simulated blood concentrations of the metabolite following single-dose administration of diazepam are lower than the observed blood concentrations. Such findings may reflect intersubject variability and/or residual amounts of desmethyldiazepam from a previous dose due to the 1-week washout period between doses and the half-life of the metabolite. These findings indicate that the five-compartment open model for diazepam and desmethyldiazepam adequately describe the pharmacokinetic profiles of the drug and its metabolite following diazepam administration. Since the same parameter estimates sufficiently described both the single-dose and chronic-dose blood–concentration time profiles of diazepam and desmethyldiazepam, it may be concluded that there was no enzyme induction or inhibition of the drug in this study.

The pharmacokinetic profiles of diazepam and its metabolite following administration of diazepam and profiles of desmethyldiazepam following administration of its prodrugs have been reported by numerous investigators. However, there are no studies in the literature comparing the pharmacokinetic profiles of desmethyldiazepam when formed as a metabolite of diazepam or as a metabolite of clorazepate in the same subjects. In determining the pharmacokinetic profile of the metabolite following clorazepate administration, it was assumed that clorazepate, at normal GI pH, is completely hydrolyzed to desmethyldiazepam, and that the resulting desmethyldiazepam was completely absorbed (10). Therefore,

Table III—Pharmacokinetic Parameters Resulting from the Five-Compartment Model in Four Subjects From Study A [a]

Subject	$\bar{C}_1^{ss}$, μg/ml	$\bar{C}_4^{ss}$, μg/ml	V_{cD}	V_{cDD} [b]	K_{Mel}, hr^{-1}	K_{14}, hr^{-1}	f_m
1	0.17	0.15	29.8	45.6	0.041	0.06	0.50
2	0.14	0.11	17.4	45.6	0.041	0.08	0.37
3	0.17	0.12	32.6	45.6	0.041	0.04	0.47
4	0.16	0.12	20.0	45.6	0.041	0.07	0.51

[a] Study A is from Ref. 6, Headings refer to the mean steady-state concentrations of diazepam ($\bar{C}_1^{ss}$) and desmethyldiazepam ($\bar{C}_4^{ss}$), volumes of compartments 1 (V_{cD}) and 4 (V_{cDD}), elimination rate of desmethyldiazepam (K_{Mel}, mean values from Table I), formation rate of desmethyldiazepam (K_{14}, calculated using Eq. 3), and the fraction (f_m, K_{14}/K_{TOT}) of diazepam metabolized to desmethyldiazepam.

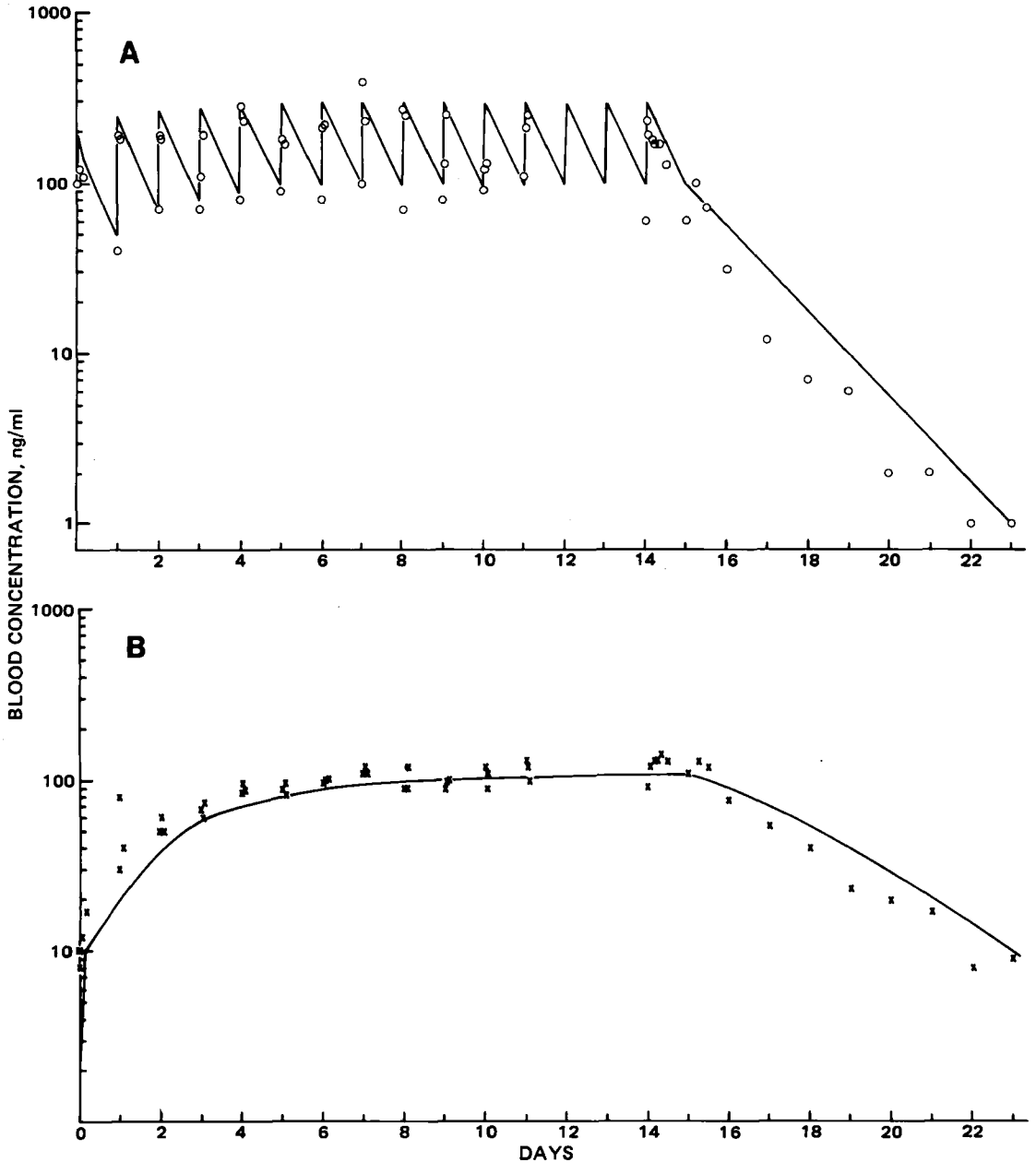

Figure 3—*Blood concentration–time profile of diazepam (A) and desmethyldiazepam (B) following once daily oral administration of 10 mg of diazepam for 15 days to a normal subject (solid lines represent simulated diazepam and desmethyldiazepam blood concentration–time profiles).*

the mean values of the desmethyldiazepam pharmacokinetic parameters following the administration of clorazepate to a normal subject population were used as parameter estimates.

Based on the initial estimates of the metabolite pharmacokinetic parameters, following clorazepate administration, the fraction (f_m) of diazepam metabolized to desmethyldiazepam was estimated to be ~0.5 by two different methods. Similar results were reported by Dasberg (17) following the chronic administration of 5 mg of diazepam and desmethyldiazepam to the same subjects in a double-blind, cross-over study. Similar results were also obtained in the cat following single-dose administration of both the drug and metabolite (18).

Model Adapted for Cerebrospinal Fluid Concentration–Time Data—This five-compartment open model may be readily adapted to predict the concentrations of diazepam and desmethyldiazepam in cerebrospinal fluid (CSF) following the administration of diazepam. Greenblatt *et al.* (19), Hallstrom *et al.* (20), Kanto *et al.* (21), and Hendel (22) have shown that the concentrations of the drug and its metabolite in CSF are in equilibrium with the unbound plasma concentrations of these compounds for the time course of the plasma concentration profile. Therefore by correcting the plasma concentrations of diazepam for protein binding, the CSF concentrations, which are presumed to reflect drug concentrations at the site of action, may be predicted.

Following single-dose administration, the concentrations of diazepam and desmethyldiazepam in CSF were simulated and are shown in Fig. 4. The model indicates that the concentration of the drug is greater than the concentration of the metabolite in CSF for the first 24 hr postadministration, suggesting that the clinical effects observed following a single-dose administration of diazepam must be attributed primarily to

Table IV—Observed and Calculated CSF Concentrations (ng/ml) of Diazepam and Desmethyldiazepam in Five Patients Following Long-Term Diazepam Therapy

Subject	Observed		Calculated
	Diazepam	Desmethyldiazepam	Desmethyldiazepam
1	22	56	55
2	30	49	75
3	14	39	35
4	21	42	50
5	28	68	70

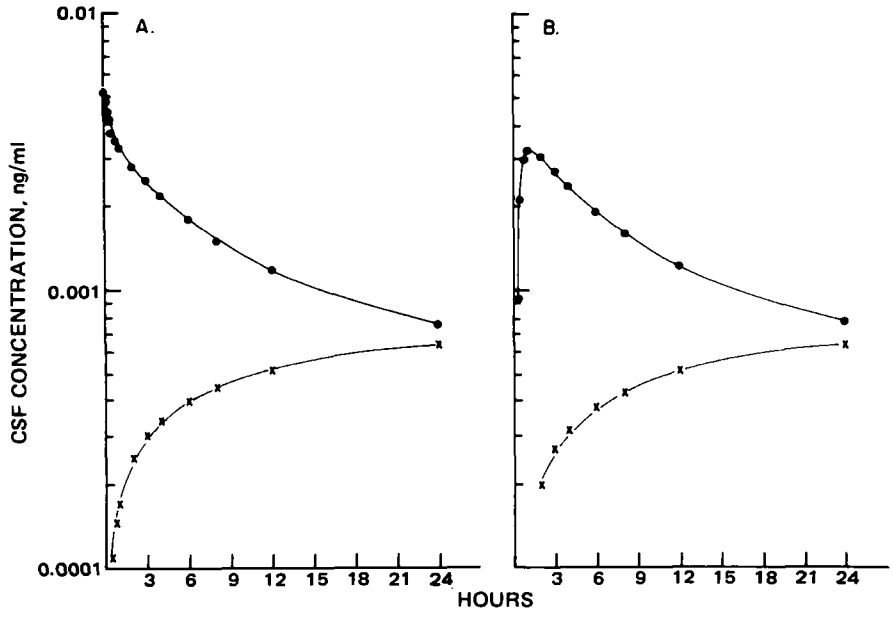

Figure 4—*Simulated CSF concentration–time profiles of diazepam (●) and desmethyldiazepam (×) following single-dose 10-mg intravenous (A) and oral (B) administrations of diazepam to a normal subject.*

diazepam and not desmethyldiazepam. Following chronic administration, the concentration of the metabolite in CSF at steady state will be equivalent to or greater than the concentration of the drug in CSF (Fig. 5). Therefore, at steady state the desmethyldiazepam will contribute significantly to the pharmacological activity observed following chronic administration of diazepam.

Hendel has reported that desmethyldiazepam accumulates in the CSF of patients treated with diazepam for several months (22). However, the metabolite CSF concentrations were calculated using the five-compartment model with the reported drug CSF concentrations in these patients corrected by the factor 2.52 (Table IV). This factor is the result of the product of 1.26 and 2; 1.26 is the relative accumulation factor for desmethyldiazepam with respect to diazepam in plasma at steady state as reported by Greenblatt *et al.* (23), and 2 is the difference in desmethyldiazepam free fraction compared with diazepam free fraction (24). The calculated CSF concentrations of metabolite at steady state are in good agreement with the observed CSF concentrations, suggesting that accumulation of this metabolite following chronic administration of diazepam is predictable.

CONCLUSION

A five-compartment open model describing the pharmacokinetic profile of diazepam and its metabolite, desmethyldiazepam, following the administration of diazepam has been developed. The pharmacokinetic parameters for desmethyldiazepam obtained following the oral administration of clorazepate adequately described the pharmacokinetics of this metabolite following diazepam administration. The parameter estimates and model simulations suggest that ~50% of the administered diazepam dose is metabolized to desmethyldiazepam. This finding suggests that the formation rate for the metabolite is approximately one-half of the total elimination rate for the drug; *i.e.*, $K_{14} = 0.06\ hr^{-1}$ whereas $K_{TOT} = 0.12\ hr^{-1}$. Overall, the single-dose pharmacokinetic parameters of diazepam following its administration and the single-dose

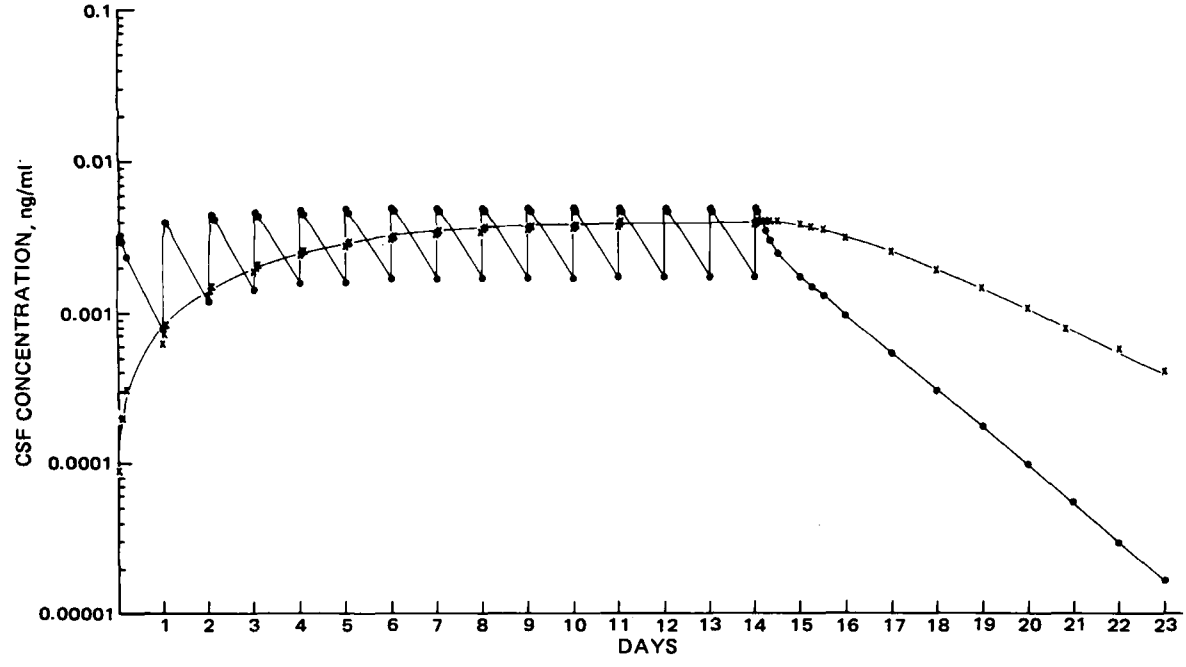

Figure 5—*Simulated CSF concentration–time profiles of diazepam (●) and desmethyldiazepam (×) following once daily chronic oral administration of 10 mg of diazepam for 15 days to a normal subject.*

pharmacokinetics of desmethyldiazepam following the administration of clorazepate can be used to describe the blood concentration–time profiles of diazepam and desmethyldiazepam following both single-dose and chronic administration of the drug, suggesting that there is no enzyme induction or inhibition of diazepam metabolism following multiple-dose administration. This model has also been adapted to predict the concentrations of diazepam and desmethyldiazepam in CSF following the administration of diazepam.

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In Vivo Release of Norethindrone Coupled to a Biodegradable Poly(α-amino acid) Drug Delivery System

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Abstract □ The *in vivo* release of norethindrone from a biodegradable steroid–polymer conjugate was studied in rats. The drug–polymer conjugate, consisting of [^{3}H]norethindrone coupled *via* a 17-carbonate bond to poly-N^5-(3-hydroxypropyl)-L-glutamine was administered to female rats by subcutaneous injection. The *in vivo* release of steroid, determined by measuring the daily radioactivity output in urine and feces, was fairly constant though it showed a gradual decrease during the 9-month study period. The data indicate that this biodegradable norethindrone–polymer conjugate is a potential candidate for the controlled delivery of norethindrone to effect long-term contraception.

Keyphrases □ Norethindrone—sustained release, biodegradable steroid–polymer conjugate, *in vivo* release rate □ Delivery systems—sustained release of norethindrone, biodegradable steroid–polymer conjugate, *in vivo* release rate □ Contraceptives—norethindrone, sustained release, biodegradable steroid–polymer conjugate, *in vivo* release rate

Although controlled release of drugs at uniform predictable rates from various drug dosage forms has been an object of considerable research for many years, the use of synthetic polymeric materials in the design of controlled-release devices is of recent origin. Of major interest has been the incorporation of contraceptive progestins into various polymers to form controlled, sustained-release drug delivery systems. The use of monolithic devices of poly(dimethylsiloxane) with progestins has been the subject of numerous reports (1–8). These devices, however, have the disadvantage of requiring implantation and removal. Furthermore, significant foreign-body reactions were observed in tissues surrounding these implants, which may be the cause of difficulty in achieving prolonged, constant release of progestins from these devices. Alternatively, the "Uterine Progesterone System" has been the subject of several studies (9–11). The safety and effectiveness of this device has been well established (9, 10, 12). Hydrogel polymers, *e.g.*, poly(hydroxyethyl methacrylate), have also been used to prepare sustained-release devices for progestins (13, 14) with favorable results.

Recently, biodegradable polymers as carriers for controlled, sustained release of various drugs have been evaluated. These polymers are synthesized from monomers which are composed of normal body constituents or which exhibit good compatibility with the body physiology. Various biodegradable polymers have been prepared for the controlled release of contraceptive steroids (15–19). The materials employed for these studies are poly(lactic acid) (15, 16), glutamic acid–leucine copolymer (17), and polyesters of homo- or copolymers of glycolide, DL-lactide, ϵ-caprolactone, or DL-ϵ-decalactone (18). Studies on the *in vitro* and *in vivo* hydrolysis of homopolymers of δ-benzyl-L-glutamate have been reported (20, 21). The

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