CONCLUSION

The spectrum of *in vitro* activity exhibited by a significant number of the mesoionic thiazolo[3,2-*a*]pyrimidiones, I, and mesoionic thiadiazolo[3,2-*a*]pyrimidiones, II, suggests that these compounds should be considered a new and novel class of antibacterial agents. Several features of these compounds are significant. While they inhibited the growth of both Gram-negative and Gram-positive bacteria *in vitro*, no activity was displayed against *E. coli*. Furthermore, a number of the mesoionic compounds exhibited comparable or greater activities, as evidenced by their zones of inhibition, than several of the sulfa drugs or nitrofurans employed as standards.

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ACKNOWLEDGMENTS AND ADDRESSES

Received April 2, 1973, from the *Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo, Buffalo, NY 14214*

Accepted for publication July 2, 1973.

Abstracted from a dissertation to be submitted by R. A. Glennon to the Graduate School, State University of New York at Buffalo, in partial fulfillment of the Doctor of Philosophy degree requirements.

Supported in part by a training grant (5-T1-GM-55-08) from the Division of Medical Sciences, U. S. Public Health Service, Bethesda, MD 20014

The authors thank Dr. Zdzislaw F. Chmielewicz, Department of Biochemical Pharmacology, for many helpful discussions, and Dr. Joseph M. Merrick, Department of Microbiology, for the donation of a culture of *Pseudomonas aeruginosa*.

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Pharmacokinetic Profile of Diazepam in Man following Single Intravenous and Oral and Chronic Oral Administrations

S. A. KAPLAN▲, M. L. JACK, K. ALEXANDER, and R. E. WEINFELD

Abstract □ Four subjects each received single intravenous and oral 10-mg. doses of diazepam and 10 mg. orally every 24 hr. for 15 days. The intravenous blood level data were fitted with a three-compartment open-model system containing both a "shallow" and a "deep" peripheral compartment. The "apparent" half-life of elimination of diazepam following intravenous administration ranged from 21 to 37 hr., and the calculated volume of distribution ranged from 160 to 205% of body weight. The rate at which diazepam returns to the central compartment from the deep peripheral compartment, k_{31}, was shown to be the rate-controlling factor in the elimination of diazepam and in the formation of desmethyldiazepam. Orally administered diazepam was rapidly and completely absorbed. Following chronic administration of 10 mg. diazepam every 24 hr., the minimum and maximum steady-state (plateau) levels of diazepam can be successfully predicted or calculated utilizing the pharmacokinetic parameters obtained following intravenous administration. Diazepam blood levels plateau at approximately Day 7 of treatment at twice the blood levels observed on Day 1. Desmethyldiazepam blood levels are within the range of the diazepam blood levels and exhibit an apparent half-life range from 50 to 99 hr. after the last dose of diazepam on Day 15.

Keyphrases □ Diazepam—pharmacokinetic profiles after single intravenous and oral and chronic oral administrations, man □ Pharmacokinetic profiles—diazepam after single intravenous and oral and chronic oral administrations, man □ Absorption kinetics—diazepam after single intravenous and oral and chronic oral administrations, man

Diazepam[1], 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 states as well as for the relief of skeletal muscle spasms (1–8).

The drug exhibits a low aqueous solubility of 50 mcg./ml. and a pKa of 3.4 (9). The transfer characteristics of diazepam across the everted rat intestinal sac are consistent with good absorbability (10). This suggests that, once in solution, the permeability (absorbability) of diazepam across the GI mucosa will not be a rate-limiting factor following oral administration of the drug.

The major metabolic pathways of diazepam (Scheme I) have been described in various animal species and in man (11–17). In man, the major metabolite measurable in the bloodstream is desmethyldiazepam. In the urine, the glucuronide conjugate of oxazepam is the major detectable metabolite (11).

The present study was designed to elucidate the

[1] Valium, containing diazepam as its active ingredient (Hoffmann–La Roche Inc., Nutley, N. J.), was administered throughout the study.

Table I—Blood Levels of Diazepam and Desmethyldiazepam (Micrograms per Milliliter) following a Single Intravenous and Oral 10-mg. Dose of Diazepam

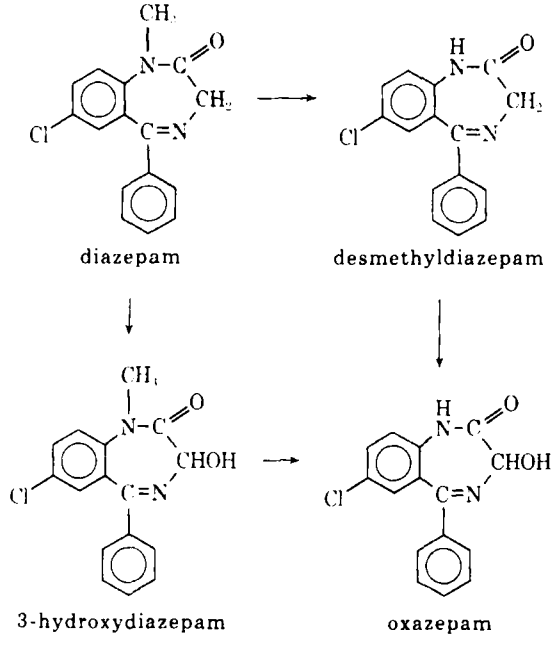
Time	Subject 1				Subject 2				Subject 3				Subject 4			
	Intravenous		Oral		Intravenous		Oral		Intravenous		Oral		Intravenous		Oral	
	D.[a]	D.D.[b]	D.	D.D.	D.	D.D.	D.	D.D.	D.	D.D.	D.	D.D.	D.	D.D.	D.	D.D.
1 min.	0.132	N.M.[c]	—	—	0.574	N.M.	—	—	0.194	—	—	—	0.338	N.M.	—	—
2.5 min.	0.323	N.M.	—	—	0.298	N.M.	—	—	0.257	N.M.	—	—	0.452	N.M.	—	—
5 min.	0.276	N.M.	—	—	0.286	N.M.	—	—	0.294	0.001	—	—	0.414	0.002	—	—
10 min.	0.263	N.M.	—	—	0.262	N.M.	—	—	0.253	0.002	—	—	0.325	0.002	—	—
15 min.	[d]	—	0.007	0.019	—	—	0.005	0.009	—	—	0.026	0.005	—	—	0.045	0.005
20 min.	0.207	N.M.	—	—	0.204	0.001	—	—	0.221	0.003	—	—	0.266	0.005	—	—
30 min.	0.174	N.M.	0.023	0.019	0.180	0.001	0.100	0.008	0.230	0.003	0.113	0.007	0.212	0.005	0.113	0.005
45 min.	0.144	0.002	0.056	0.018	0.151	0.004	0.153	0.011	0.201	0.004	0.166	0.011	0.181	0.006	0.163	0.011
1 hr.	0.118	0.001	0.063	0.014	0.135	0.005	0.169	0.014	0.184	0.005	0.189	0.011	0.198	0.006	0.173	0.010
1.5 hr.	0.107	0.004	0.137	0.020	0.112	0.006	0.135	0.014	0.150	0.006	0.175	0.014	0.152	0.008	0.155	0.013
2 hr.	0.092	0.005	0.109	0.022	0.093	0.007	0.103	0.015	0.142	0.008	0.146	0.014	0.153	0.011	0.128	0.016
3 hr.	0.074	0.006	0.090	0.028	0.074	0.007	0.082	0.016	0.145	0.012	0.126	0.017	0.141	0.014	0.109	0.018
4 hr.	0.066	0.007	0.084	0.031	0.067	0.008	0.072	0.018	0.139	0.015	0.114	0.018	0.130	0.016	0.098	0.020
6 hr.	0.047	0.008	0.070	0.032	0.053	0.009	0.061	0.020	0.107	0.017	0.103	0.022	0.106	0.019	0.096	0.023
8 hr.	0.045	0.008	0.066	0.033	0.049	0.014	0.047	0.021	0.089	0.019	0.095	0.021	0.072	0.018	0.078	0.026
12 hr.	0.031	0.010	0.046	0.028	0.041	0.017	0.034	0.022	0.061	0.019	0.069	0.023	0.049	0.027	0.061	0.030
24 hr.	0.032	0.012	0.043	0.031	0.030	0.020	0.029	0.025	0.040	0.027	0.039	0.025	0.036	0.031	0.038	0.033
30 hr.	0.030	0.014	0.037	0.030	0.026	0.021	0.026	0.026	0.039	0.033	0.039	0.027	0.022	0.025	0.033	0.037
48 hr.	0.028	0.019	0.036	0.035	0.018	0.021	0.020	0.017	0.025	0.029	0.025	0.030	0.023	0.039	0.018	0.027

[a] D. = diazepam. [b] D.D. = desmethyldiazepam. [c] N.M. = below 0.001 mcg./ml. [d] — = no specimen obtained.

pharmacokinetic profile of diazepam in man following intravenous administration and to evaluate the physiological availability and disposition following single oral and chronic oral administrations of the drug.

EXPERIMENTAL

Clinical Protocol—Four healthy male volunteers, ages 25–43, each received a single 10-mg. dose of diazepam administered intravenously and orally 1 week apart[2]. Commencing 1 week thereafter, each subject received a 10-mg. oral dose of diazepam 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 the 1st hr. postadministration.



Scheme I—Major metabolic pathways of diazepam

[2] The clinical aspects of the study were conducted at the Deer Lodge Research Unit, Deer Lodge, Mont., under the direction of Dr. James D. Moore.

Blood specimens were obtained at the time intervals indicated in Tables I and II for each treatment. The total volumes of urine voided were collected at 24-hr. intervals from −24 to 0, 0 to 24, and 24 to 48 hr. postadministration following the single intravenous and oral administrations. All specimens were frozen for subsequent analysis.

Analytical Method—Blood and urine specimens were analyzed for diazepam and desmethyldiazepam by the electron-capture GLC procedure of de Silva and Puglisi (18), with a sensitivity of 0.001 mcg./ml. for each component using a 1-ml. specimen.

RESULTS AND DISCUSSION

The diazepam and desmethyldiazepam blood level data following the single-administration studies are presented in Table I for all four subjects and plotted for one subject in Fig. 1. The blood level data following the chronic administration studies are presented in Figs. 2–5. The pharmacokinetic profile following the single intra-

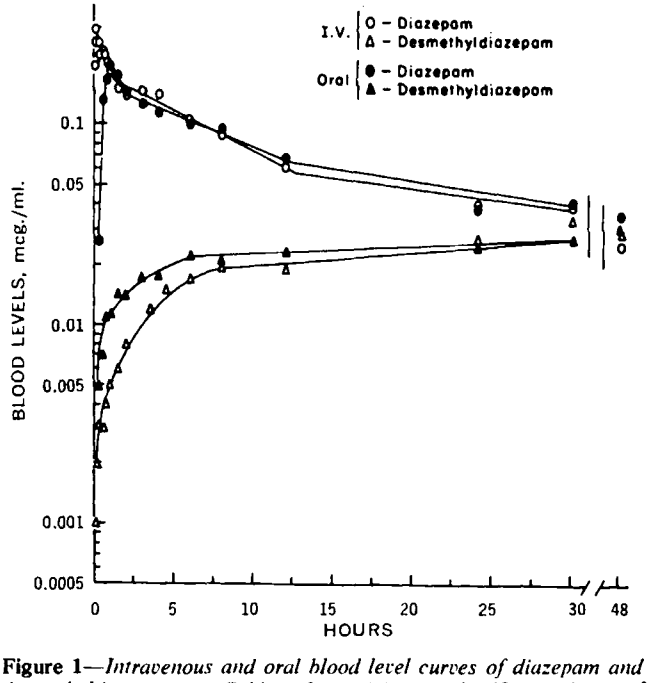


Figure 1—*Intravenous and oral blood level curves of diazepam and desmethyldiazepam in Subject 3 receiving single 10-mg. doses of diazepam.*

Table II—Pharmacokinetic Profile of Diazepam in Man following Single Intravenous Administration to Four Subjects

	Subject			
	1	2	3	4
Dose, mg.	10	10	10	10
Dose, mg./kg.	0.113	0.118	0.153	0.157
Subject weight, kg.	88.5	84.9	65.4	63.6
Subject age, years	41	31	25	43
P, mcg./ml.	0.177	0.346	0.089	0.282
A, mcg./ml.	0.107	0.171	0.140	0.156
B, mcg./ml.	0.052	0.058	0.078	0.061
π (hr.$^{-1}$), 0.693/π (hr.)	3.12, 0.22	22.43, 0.03	3.36, 0.21	4.78, 0.14
α (hr.$^{-1}$), 0.693/α (hr.)	0.472, 1.5	0.734, 0.94	0.210, 3.3	0.226, 3.1
β (hr.$^{-1}$), 0.693/β (hr.)	0.019, 36.5	0.026, 26.7	0.024, 28.9	0.021, 33.0
Percent volume central compartment[a]	33.7	20.5	49.8	31.4
Percent volume of distribution[a]	196.4	182.9	160.9	205.3
k_{12}, hr.$^{-1}$	1.14	12.35	0.88	2.39
k_{21}, hr.$^{-1}$	1.66	9.27	2.43	2.18
k_{13}, hr.$^{-1}$	0.55	1.14	0.12	0.24
k_{31}, hr.$^{-1}$	0.15	0.20	0.090	0.076
k_{el}, hr.$^{-1}$	0.111	0.228	0.078	0.137
Ratio β/k_{el}	0.17	0.11	0.30	0.15
Area under blood level curve, mcg./ml./hr.	1.886	1.853	2.822	2.556
Percent of dose in 0–48-hr. urine as:				
Intact diazepam	<0.05	<0.05	<0.05	<0.05
Intact desmethyldiazepam	<0.05	<0.05	<0.05	<0.05
Conjugated desmethyldiazepam	4.8	5.2	5.7	9.2

[a] Calculated as percent body weight.

venous and oral administrations of diazepam are summarized in Tables II and III, respectively.

Following the intravenous administration of diazepam, a triexponential blood level curve was observed in all four subjects as exemplified for Subject 3 in Fig. 1. The pharmacokinetic profile of diazepam was determined utilizing the data obtained following the intravenous administration of the drug. The data suggested that the pharmacokinetic evaluation would require minimally a three-compartment open-model system (19). The first two exponential phases with rate constants π and α reflect two different types of distribution phenomena, *i.e.*, distribution from the central compartment into a rapidly equilibrating or "shallow" peripheral compartment and a slowly equilibrating "deep" peripheral compartment. The third exponential phase, with a rate constant β, is referred to as the "apparent" elimination rate of the drug from the body. All three rate constants, π, α, and β, are hybrid first-order rate constants, each influenced by all of the individual processes involved in the disposition of the drug.

Solution of the differential equations of the three-compartment open model (Scheme II) yields the following integrated equation describing the blood level–time curve after intravenous administration:

$$(C_p)_t = Pe^{-\pi t} + Ae^{-\alpha t} + Be^{-\beta t} \qquad \text{(Eq. 1)}$$

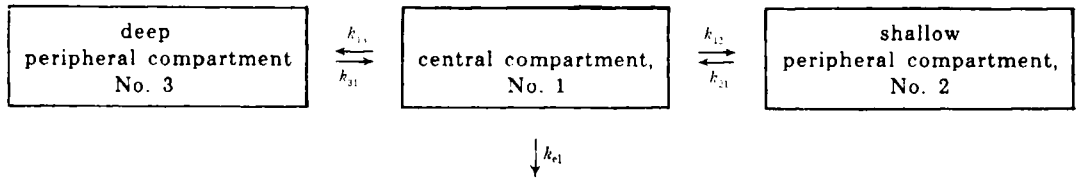
where $(C_p)_t$ is the concentration of drug in the blood at time t, and P, A, and B are the ordinate axis intercepts. The individual rate constants of the model, k_{12}, k_{21}, k_{13}, k_{31}, and k_{el}, are calculable from P, A, B, π, α, and β (20). These rate constants do not necessarily apply to any anatomically defined tissue compartments but are meaningful in defining the disposition of drug from the central compartment.

The total volume of distribution of diazepam (21), V_d, was found to be 196, 183, 161, and 205% of body weight for Subjects 1 through 4, respectively, following a 10-mg. intravenous administration of diazepam. The volume of the central compartment, V_p, was calculated to be 33.7, 20.5, 49.8, and 31.4% of body weight for Subjects 1 through 4, respectively. The size of the central compartment is consistent with the utilization of a three-compartment open pharmacokinetic model system in which elimination is occurring from the central compartment (22).

The intravenous blood level data were fitted to the triexponential equation by means of a "nonlinear" regression analysis computer program (23). The pharmacokinetic parameters of diazepam obtained for each subject following intravenous administration are summarized in Table II. The rate constants associated with the rapidly and slowly equilibrating sites in the peripheral compartments ranged from 3.1 to 22.4 hr.$^{-1}$ for π and from 0.21 to 0.73 hr.$^{-1}$ for α, respectively. These values correspond to apparent half-life ranges of 2–13 min. and 0.95–3.1 hr., respectively. The overall elimination rate constant, β, ranged from 0.019 to 0.026 hr.$^{-1}$, corresponding to an apparent half-life range of 26.7–36.5 hr. The magnitude of the three hybrid rate constants, π, α, and β, reflect an extremely rapid initial distribution of diazepam and a slow apparent elimination rate of drug from the body.

Table III—Pharmacokinetic Profile of Diazepam in Man following Single Oral Administrations to Four Subjects

	Subject			
	1	2	3	4
Dose, mg.	10	10	10	10
Dose, mg./kg.	0.113	0.118	0.153	0.157
Subject weight, kg.	88.5	84.9	65.4	63.6
Subject age, years	41	31	25	43
B, mcg./ml.	0.067	0.048	0.086	0.089
β (hr.$^{-1}$), 0.693/β (hr.)	0.015, 46.2	0.019, 36.5	0.027, 25.7	0.33, 21.0
Area under blood level curve, mcg./ml./hr.	2.272	1.670	2.728	2.389
Blood level curve area ratio, oral/i.v.	1.205	0.901	0.967	0.935
Absorption rate constant, hr.$^{-1}$	1.68	1.9	2.5	1.58
Blood level peak height, mcg./ml.	0.137	0.169	0.189	0.173
Blood level peak time, hr.	1.5	1	1	1
Percent of dose in 0–48-hr. urine as:				
Intact diazepam	<0.05	<0.05	<0.05	<0.05
Intact desmethyldiazepam	<0.05	<0.05	<0.05	<0.05
Conjugated desmethyldiazepam	2.5	5.1	6.1	2.6



Scheme II—Three-compartment open-model pharmacokinetic system for diazepam

The individual rate constants, k_{12}, k_{21} and k_{13}, k_{31}, reflect the rate of distribution into and out of the shallow and deep peripheral compartments, respectively. The mean ratio of k_{21}/k_{12} of 1.4, reflecting return and entry of drug within the shallow peripheral compartment, suggests rapid equilibration and relatively free transfer of drug between the central and shallow compartments. The mean ratio of k_{31}/k_{13} of 0.3, reflecting return and entry of drug within the deep peripheral compartment, suggests slow equilibration plus drug binding to tissue or protein sites in this compartment, with a corresponding slow return of drug to the central compartment.

The magnitude of k_{31} was small within each subject. This rate constant represents the rate of return of drug from the deep peripheral compartment to the central compartment. This finding suggests that the rate-controlling step in the elimination of diazepam from the body is the rate at which the drug is released from the deep peripheral compartment. The mean ratio of β/k_{el} of 0.18 indicates that only 18% of the diazepam in the body is in the central compartment, available for elimination at any time (24).

By using the rate constants obtained following intravenous administration (Table II), the drug levels in the central and the two peripheral compartments were simulated for each subject (Fig. 6). These simulations clearly show that the deep peripheral compartment contains more diazepam than either the central or shallow peripheral compartment. This finding emphasizes the importance of the return of drug to the central compartment from the deep peripheral compartment as the rate-controlling step in the overal elimination profile of diazepam.

Following the intravenous administration of diazepam, desmethyldiazepam was detected in the blood. Initially, desmethyldiazepam is formed rapidly but then, at approximately 12 hr. postadministration, there is an apparent change in the formation rate constant; the blood levels of desmethyldiazepam continue to rise but very slowly. This slower apparent formation rate constant of desmethyldiazepam was calculated directly from the desmethyldiazepam blood level data after the 12-hr. data point by the method of least squares and found to be essentially equal to the overall elimination rate constant, β, of diazepam in each subject. The initial apparent formation rate constant of desmethyldiazepam was determined by "feathering" (24) the initial portion of the desmethyldiazepam blood level curve. The rate constants are reported in Table IV. Such findings indicate that the overall elimination of diazepam occurs almost exclusively *via* the desmethyldiazepam pathway and that the formation of desmethyldiazepam is, in turn, rate dependent upon the return of diazepam from the deep peripheral compartment.

Overall, the pharmacokinetic profile indicates that k_{31}, the rate of return of drug from the deep peripheral compartment, and not k_{el}, the true elimination rate constant, is the rate-controlling factor in the elimination of diazepam from the body. Therefore, the characteristics of the deep peripheral compartment would be of importance relative to understanding the physiological disposition character-

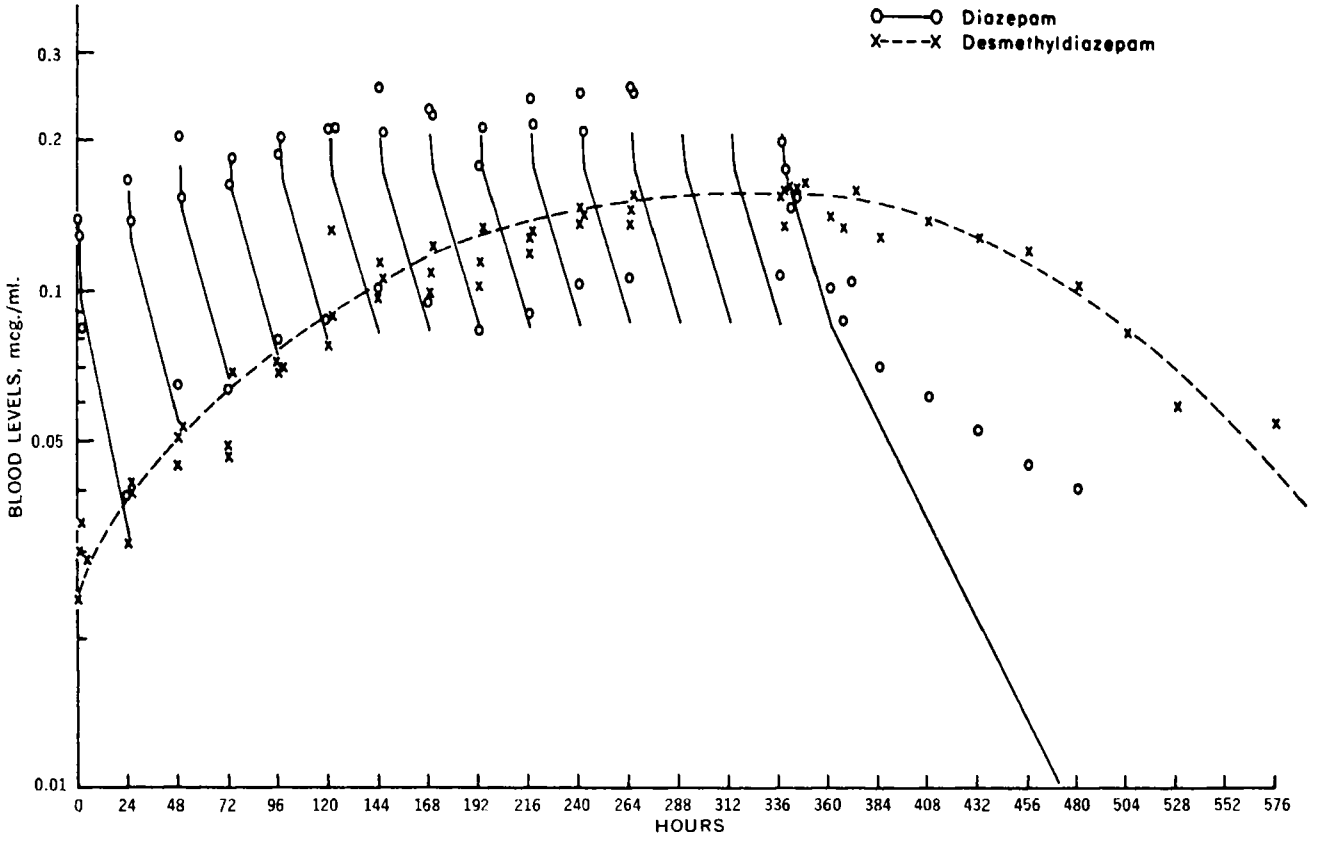


Figure 2—*Oral blood level data of diazepam and desmethyldiazepam in Subject 1 receiving 10 mg. diazepam every 24 hr. for 15 days (solid line represents calculated diazepam blood level curve).*

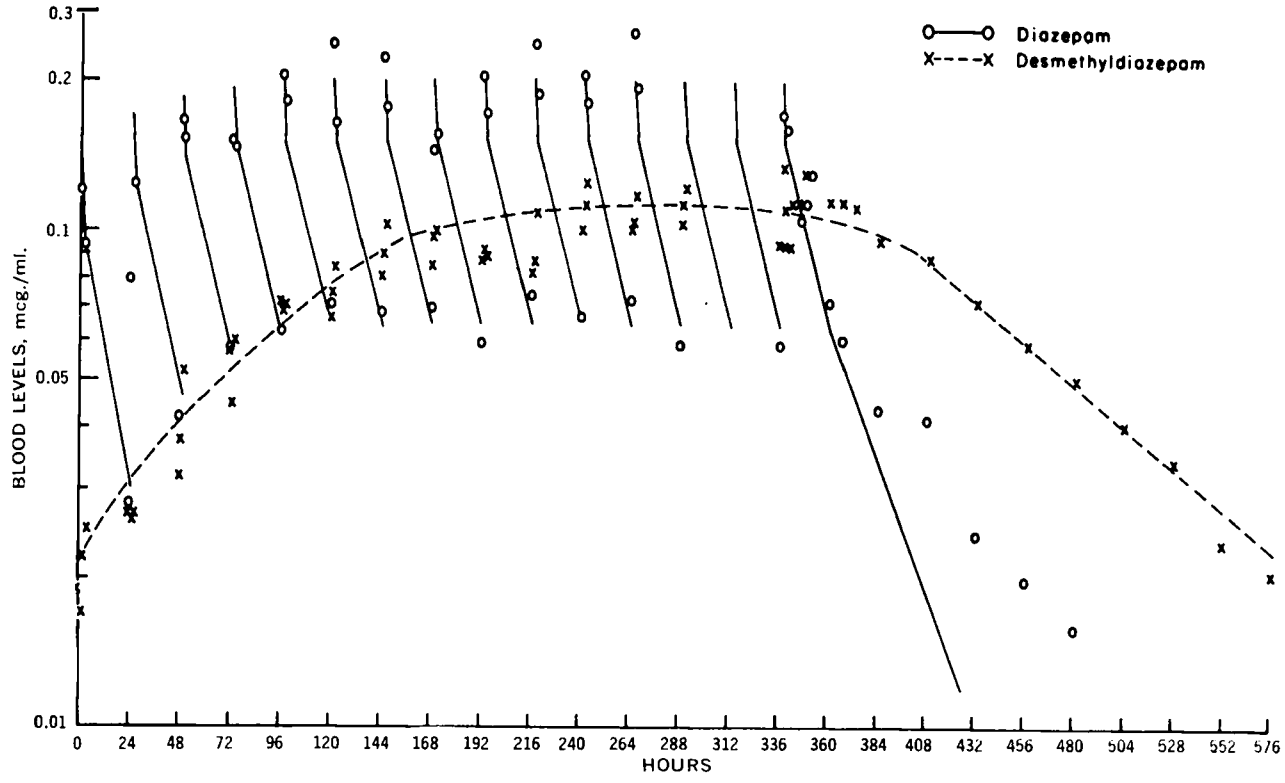


Figure 3—*Oral blood level data of diazepam and desmethyldiazepam in Subject 2 receiving 10 mg. diazepam every 24 hr. for 15 days (solid line represents calculated diazepam blood level curve).*

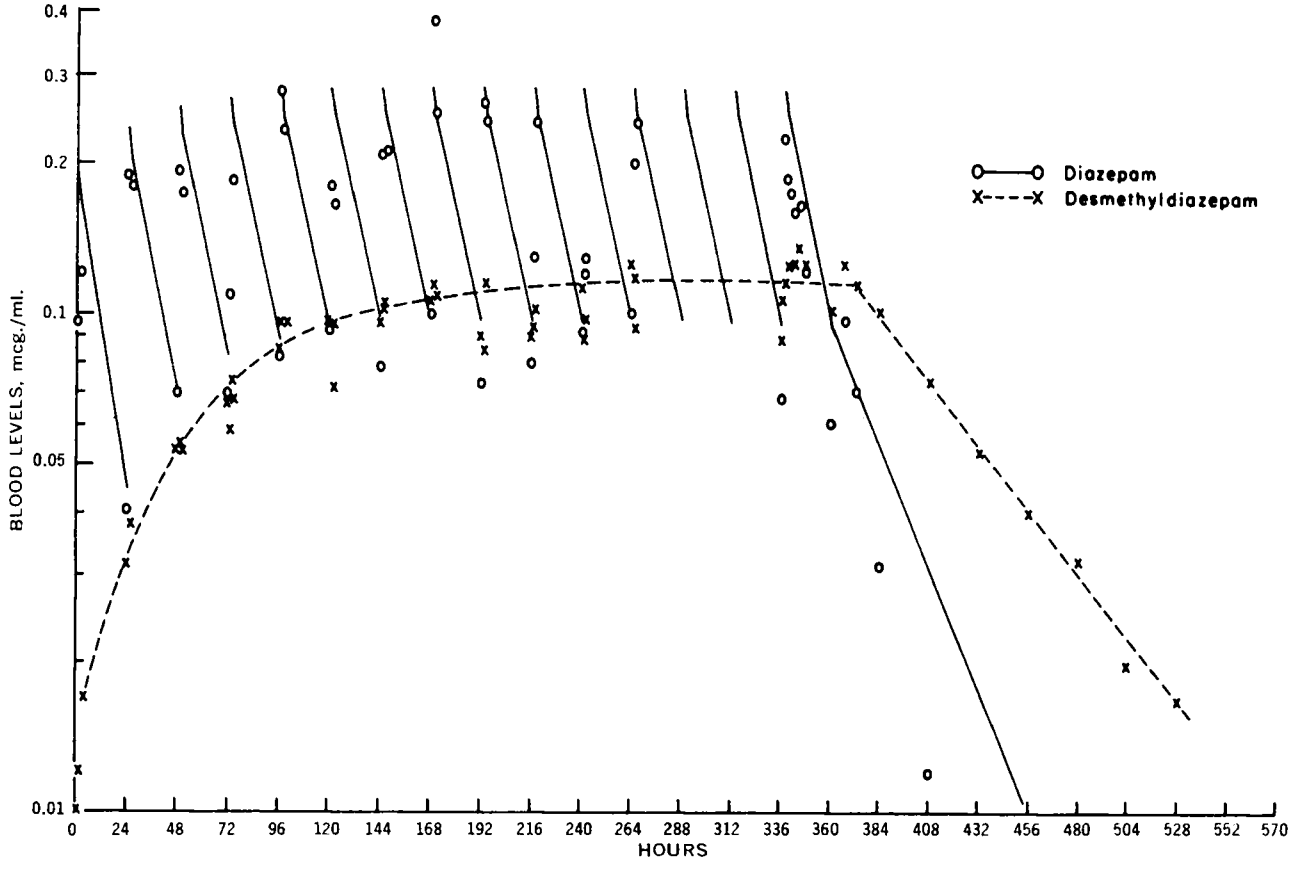


Figure 4—*Oral blood level data of diazepam and desmethyldiazepam in Subject 3 receiving 10 mg. diazepam every 24 hr. for 15 days (solid line represents calculated diazepam blood level curve).*

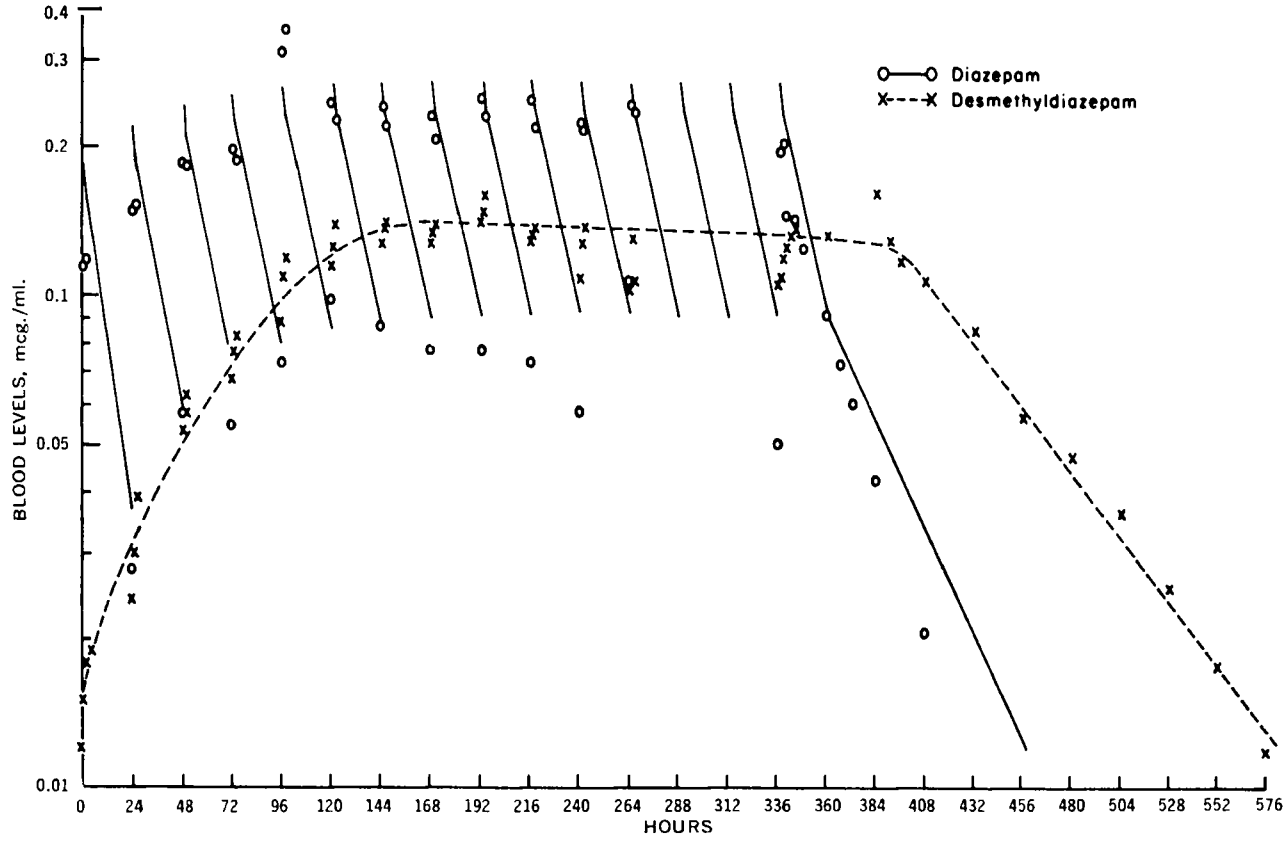


Figure 5—*Oral blood level data of diazepam and desmethyldiazepam in Subject 4, receiving 10 mg. diazepam every 24 hr. for 15 days (solid line represents calculated diazepam blood level curve).*

istics of diazepam in man. Alterations in the binding characteristics of drug to tissues or proteins associated with this compartment may yield marked alterations in the pharmacokinetic profile of the drug, whereas factors that affect the metabolism *per se* (*e.g.*, in the liver) may only minimally affect this pharmacokinetic profile.

Van der Kleijn (26) reported that diazepam is extensively protein bound in the dog. By using whole body autoradiography, he also showed that certain tissues, *i.e.*, brain, kidney, liver, myocardium, and digestive system, show large and rapid uptake of radioactive diazepam following the intravenous administration of diazepam to mice (27). These same tissues, in turn, show a very slow decline of diazepam levels. Although there was a rapid uptake of drug by the adipose tissues, there was a corresponding rapid decline of drug in these tissues, suggesting that drug is not strongly bound to adipose tissue. The observed extensive protein binding and the slow release of diazepam from tissues such as the brain, heart, and digestive system are consistent with the deep compartment of the proposed pharmacokinetic model. The slow release of diazepam from such protein and tissue binding sites probably determines the rate of metabolism and, therefore, elimination of diazepam from the body.

Single Oral Administration—Each subject received a single 10-mg. oral dose of diazepam. The blood levels and urinary excretion data are presented in Tables I and III, respectively, for all four subjects, and the blood level data are plotted in Fig. 1 for Subject 3.

Table IV—Formation Rate Constants for Desmethyldiazepam

	Subject			
	1	2	3	4
Overall elimination rate constant of diazepam, $hr.^{-1}$	0.019	0.026	0.024	0.021
Formation rate constant of desmethyldiazepam after 12 hr., $hr.^{-1}$	0.020	0.028	0.030	0.016
Initial formation rate constant of desmethyldiazepam, $hr.^{-1}$	0.546	0.427	0.329	0.351

Following the single oral administration of 10 mg. diazepam, the blood levels peaked at 1–1.5 hr. in all four subjects, indicating rapid absorption. When using the area under the blood level curve as an index of the extent of absorption, absorption appears to be essentially complete. The ratios of the areas under the oral blood level curves to that of the areas under the intravenous blood levels are 1.2, 0.90, 0.97, and 0.94 for Subjects 1 through 4, respectively.

The overall elimination rate constant, β, calculated following oral administration of diazepam (Table III) approximates the corresponding rate constant obtained following intravenous administration of the drug in each subject.

The evaluation of the oral diazepam blood level data relative to peak heights, peak times, areas under the blood level curves, and the first-order absorption rate constant (28) indicates that diazepam is rapidly and completely absorbed following oral administration in man. In addition, the physiological disposition characteristics do not appear to be dependent upon the route of administration. These characteristics are further confirmed by the similarity of the blood level curves of the metabolite desmethyldiazepam, determined following the intravenous and oral administration of diazepam.

The urinary excretion data following the single intravenous and oral administration of diazepam are presented in Tables II and III. Less than 0.05% of the administered dose was recovered in the urine as intact diazepam, indicating complete biotransformation of diazepam in man. The conjugated biotransformation product of desmethyldiazepam was identified in the urine, accounting for approximately 2.5–9% of the administered dose. The conjugates of oxazepam and 3-hydroxydiazepam were detected but not quantitated. Following the administration of radioactive diazepam, approximately 70% of the administered dose was reported (11, 16, 17) to be excreted in the urine and approximately 10% to be excreted in the feces.

Chronic Oral Administration—A 10-mg. dose of diazepam was administered every 24 hr. for 15 days to each of the four subjects. Blood specimens were obtained at 1, 2, and 24 hr. following each administration and analyzed for diazepam and desmethyldiazepam. The blood levels are presented in Figs. 2–5.

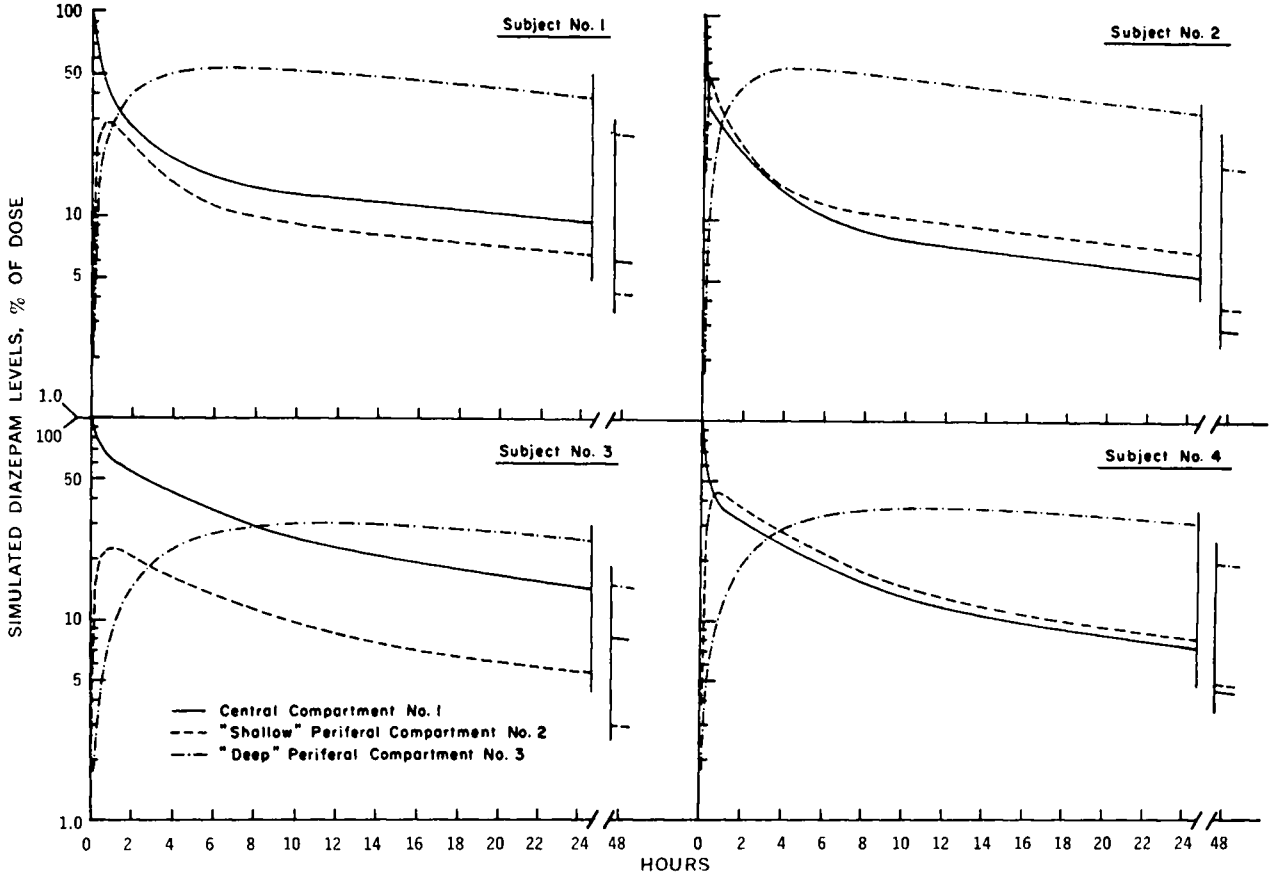


Figure 6—*Simulated compartmental drug level profile of diazepam in Subjects 1–4.*

The diazepam blood level curves following the 10-mg. oral chronic administration of diazepam to four subjects every 24 hr. were simulated by adapting the equations presented by Boxer *et al.* (29). Such an equation is applicable for diazepam because diazepam is both rapidly and completely absorbed. Since the intravenous blood level curve of diazepam is triexponential, the Boxer equation was modified to take into account the contributions of each exponential phase. Therefore, the simulated chronic oral dosing diazepam blood level curves were computed using the pharmacokinetic parameters obtained following the intravenous administration of diazepam to each subject, with the assumption that diazepam was rapidly and completely absorbed. Since the absorption rate constant is much larger than the disposition rate constants, the exponential associated with the absorption can be deleted from the blood level equation without affecting the predicted blood level profile.

Therefore, using Eq. 1 the blood level at any time, t, is the sum of the contributions of each exponential. By applying the Boxer equation for each exponential phase, the sum of the three exponentials will be the blood level at that time. The Boxer equation for a monoexponential is given by Eq. 2:

$$C_{p_n} = \frac{C_0 - C_0 r^n}{1 - r} \qquad \text{(Eq. 2)}$$

where C_{p_n} = blood level following the nth dose at time t, C_0 = initial blood level at time t, and $r = e^{-\beta\tau}$, where β is the slope of the exponential phase and τ is the dosing frequency.

For a triexponential, this equation becomes:

$$C_{p_n} = \frac{P_0 - P_0 r_1^n}{1 - r_1} + \frac{A_0 - A_0 r_2^n}{1 - r_2} + \frac{B_0 - B_0 r_3^n}{1 - r_3} \qquad \text{(Eq. 3)}$$

where P_0, A_0, and B_0 are the contributions of the respective exponentials at the initial time t, and $r_1 = e^{-\pi\tau}$, $r_2 = e^{-\alpha\tau}$, and $r_3 = e^{-\beta\tau}$.

Equation 3 was used to simulate the chronic blood level curves of diazepam for each subject. The simulated chronic diazepam blood level curves (Figs. 2–5) correspond well with the experimental blood level data points. Steady-state (plateau) diazepam blood levels were evident by the 7th day of the study. There was an approximate threefold difference between the mean maximum and minimum diazepam steady-state blood levels (Table V) observed at 1 and 24 hr. following administration, respectively.

The mean steady-state maximum and minimum blood levels were approximately twofold greater than the corresponding blood levels observed on Day 1. The calculated elimination rate constant, β, observed following the last dose on Day 15 approximated the corresponding rate constant observed following the single oral administration of the drug. This finding of relatively constant steady-state diazepam blood levels substantiates the constancy of the absorption, distribution, metabolism, and excretion with each administration of the drug, with all processes following apparent first-order kinetics. Such a steady-state profile for diazepam indicates that unpredicted drug accumulation will not occur and suggests no enzyme induction of diazepam metabolism. In their reported bioavailability data of diazepam, based on steady-state plasma levels, Berlin *et al.* (30) observed a small variation in steady-

Table V—Calculated and Experimental Diazepam Steady-State Blood Levels (Micrograms per Milliliter)

	Subject			
	1	2	3	4
Calculated minimum steady-state level	0.088	0.066	0.099	0.094
Experimental minimum steady-state level	0.104	0.068	0.085	0.078
Calculated maximum steady-state level	0.212	0.204	0.289	0.277
Experimental maximum steady-state level	0.235	0.210	0.224	0.238

state levels between subjects and half-lives of elimination consistent with the data presented herein.

The desmethyldiazepam blood level data obtained following the single intravenous and oral administrations of diazepam (Table I) do not lend themselves to pharmacokinetic evaluation. In all four subjects, the desmethyldiazepam blood levels continued to increase during the 48-hr. experimental period. In most instances, the increasing desmethyldiazepam levels were approximately equal to the declining diazepam blood levels during the 24–48-hr. interval following both intravenous and oral administrations of diazepam. As previously discussed, the formation rate of desmethyldiazepam is influenced by k_{31}, the rate at which diazepam is returning from the deep peripheral compartment to the central compartment.

Following the chronic dosing of 10 mg. diazepam every 24 hr. for 15 days, the desmethyldiazepam maximum–minimum blood level range of 0.16–0.09 mcg./ml. was within the range of the minimum steady-state diazepam blood levels (Figs. 2–5). The smaller range of maximum-to-minimum desmethyldiazepam blood levels is reflecting the slow formation and elimination rates of desmethyldiazepam. Following the last dose of diazepam on Day 15, the apparent half-life of elimination of desmethyldiazepam ranged from 50 to 99 hr. The observed slow decline in desmethyldiazepam levels after the administration of diazepam is slower than might be anticipated after desmethyldiazepam is administered due to the continued formation of the metabolites.

The overall elimination rate of diazepam, which is shown to relate directly to the formation rate of desmethyldiazepam, appears to be a major determining factor in the blood level profile of diazepam and its metabolites in various species. The more rapid the observed diazepam-to-desmethyldiazepam conversion rate, the more rapid is the onset of desmethyldiazepam blood levels. In contrast to man, the dog exhibits a conversion rate that is so rapid that diazepam is barely detected and desmethyldiazepam is essentially the exclusive blood component. In the rat, the conversion rate is negligible so the diazepam is the major blood component. The negligible desmethyldiazepam levels in the rat, however, may also be the result of the metabolic pathway to the 4-hydroxy derivatives (14, 15, 31).

SUMMARY

Four subjects each received a single intravenous and oral 10-mg. dose of diazepam and 10 mg. orally every 24 hr. for 15 days. The intravenous blood level data were fitted with a three-compartment open-model system containing both a shallow and a deep peripheral compartment. The half-lives corresponding to the third exponential are a measure of the overall elimination rate of the drug from the body and ranged from 21 to 37 hr. following intravenous administration. The volume of distribution ranged from 160 to 205% of body weight. The data suggest that the rate at which diazepam returns to the central compartment from the deep peripheral compartment, k_{31}, is the rate-controlling factor in the elimination of diazepam and in the formation rate of desmethyldiazepam.

Following oral administration, diazepam was absorbed rapidly and completely. The elimination rate observed following oral administration approximates that observed following intravenous administration.

Following the multiple oral dosing of 10 mg. diazepam every 24 hr. for 15 days, the diazepam blood levels plateau at approximately Day 7. The mean maximum–minimum diazepam plateau levels were 0.225–0.084 mcg./ml., and the half-life of elimination after the 15th dose was approximately the same as that seen following a single dose of diazepam. The corresponding desmethyldiazepam maximum–minimum levels of 0.16–0.09 mcg./ml. are within the lower range of the diazepam blood levels. The smaller range of maximum–minimum desmethyldiazepam levels results from its slow formation and elimination rate. Following the last dose of diazepam, the apparent half-life of elimination of desmethyldiazepam ranged from 50 to 99 hr.

The minimum and maximum steady-state (plateau) levels of diazepam can be successfully predicted (calculated) as a function of the pharmacokinetic parameters obtained following the intravenous administration of drug to each subject. This confirms the reproducibility of the apparent first-order absorption and physiological disposition characteristics of diazepam from administration to administration.

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ACKNOWLEDGMENTS AND ADDRESSES

Received June 5, 1973, from the *Department of Biochemistry and Drug Metabolism, Hoffmann–La Roche Inc., Nutley, NJ 07110*

Accepted for publication July 31, 1973.

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