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ACKNOWLEDGMENTS AND ADDRESSES

Received July 30, 1973, from the *Department of Biochemistry and Drug Metabolism, Hoffmann-La Roche Inc., Nutley, NJ 07110*

Accepted for publication September 14, 1973.

The authors thank Dr. H. H. Kaegi and Mr. G. Bader of the Chemical Research Department for the synthesis of clonazepam-2-^{14}C; Dr. J. C. Sheridan of the Analytical Research Department for the micronization of clonazepam; Dr. E. D. Fram and Dr. A. S. Leon for their supervision of the use of radioisotopes in the clinical study conducted at the Newark, N.J., Beth Israel Medical Center; Dr. M. A. Schwartz, Mr. C. W. Williams, and Mr. S. J. Kolis for the radiometric analysis of the specimens obtained from this clinical study; Dr. H. J. Kupferberg of the National Institute of Narcotics and Dangerous Substances, National Institutes of Health, Bethesda, Md.,, for providing the data on the blood levels of clonazepam on chronic administration; Dr. Floie Vane for the mass spectral data reported; Dr. M. A. Brooks for his advice and Mr. J. Meyer for his assistance in the polarographic studies; and Mr. R. Mc Glynn for the drawings of the figures presented.

[x] To whom inquiries should be directed.

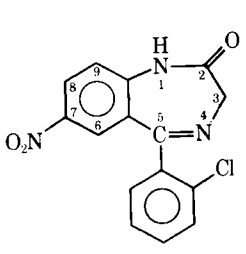
Pharmacokinetic Profiles of Clonazepam in Dog and Humans and of Flunitrazepam in Dog

S. A. KAPLAN[x], K. ALEXANDER, M. L. JACK, C. V. PUGLISI, J. A. F. de SILVA, T. L. LEE, and R. E. WEINFELD

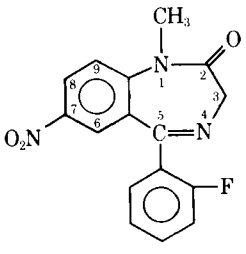
Abstract □ Clonazepam appears to be well absorbed, exhibiting peak blood levels of 6.5–13.5 ng/ml at 1–2 hr after administration in human subjects receiving 2-mg single oral doses. The "apparent" half-lives of elimination ranged from 18.7 to 39 hr in the subjects studied. Less than 0.5% of the dose is recoverable in the urine, suggesting complete biotransformation and/or alternative routes of excretion. Flunitrazepam in the dog is rapidly eliminated and exhibits a "first-pass" metabolism effect following oral administration, whereby the *N*-desmethyl metabolite is the major detectable drug component in the blood. Neither the drug nor its *N*-desmethyl metabolite is detected in the urine, suggesting extensive and complete biotransformation.

Keyphrases □ Clonazepam—blood levels and urinary excretion in dogs and humans □ Flunitrazepam—blood levels and urinary excretion in dogs □ Pharmacokinetic profiles—clonazepam in dogs and humans, flunitrazepam in dogs

The 7-nitro-1,4-benzodiazepin-2-ones, clonazepam and flunitrazepam, have shown anticonvulsant properties in several animal species (1–5). In addition, clonazepam is clinically effective in controlling minor motor seizures (petit mal) at minimal effective doses in the range of 1–2 mg/day orally (6–9). Metabolic



clonazepam



flunitrazepam

and pharmacokinetic studies of clonazepam in the rat, dog, and humans were previously reported (10). Flunitrazepam is a clinically effective hypnotic (11, 12) and an anesthesia induction agent (13, 14).

The present study reports the pharmacokinetic profile of clonazepam in the dog and humans and of flunitrazepam in the dog based on the evaluation of blood level and urinary excretion data determined using a sensitive and specific electron-capture GLC assay procedure (15). The assay follows for the measurement of clonazepam following its administration and of flunitrazepam and *N*-desmethyl flunitrazepam following flunitrazepam administration.

Table I—Pharmacokinetic Parameters Associated with Physiological Disposition of Clonazepam in the Dog

Parameters	Route of Administration and Formulation			
	Intravenous Solution	Oral Solid (Nonmicronized)	Oral Solution	Oral Tablet (Micronized)
Dose, mg	30	30	30	30
Weight, kg	13.1	13.0	13.0	13.0
Dose, mg/kg	2.3	2.3	2.3	2.3
A, ng/ml	1205	—	—	—
B, ng/ml	601	—	—	—
α, hr^{-1}	30.621	—	—	—
β, hr^{-1}	0.129	0.136	0.149	0.110
Half-life, hr	5.4	5.1	4.7	6.3
C_p^0, ng/ml	1806	—	—	—
V_p, volume of central compartment, liters	16.6	—	—	—
% V_p, % of body weight	127	—	—	—
$(V_d)\beta$, total volume of distribution, liters	29.3	—	—	—
% $V_d\,\beta$, % of body weight	224	—	—	—
k_{12}, hr^{-1}	7.780	—	—	—
k_{21}, hr^{-1}	10.283	—	—	—
k_{el}, hr^{-1}	0.384	—	—	—
Area (blood level curve), ng/ml/hr	4672	61	4486	5043
Area ratio, oral/intravenous × 100	—	1.3	96	110

Table II—Blood Level Profile of Clonazepam in Humans following Oral Administration of Single 2-mg Doses

	Subject									
	1	2	3	4	5	6	7	8	9	10
Weight, kg	71.3	77.2	79.5	64.9	81.3	96.3	66.3	83.1	96.8	75.5
Hours	Blood Levels, ng/ml									
0.5	1.8	0.6	N.M.[a]	4.3	N.M.	4.0	1.2	5.7	N.M.	1.7
1	10.7	5.7	3.3	8.3	6.2	6.6	11.3	13.5	3.7	6.1
1.5	10.7	13.0	5.9	9.7	6.7	9.0	12.6	13.2	5.4	7.4
2	10.0	11.9	6.8	12.6	6.8	10.9	10.2	9.9	6.5	6.9
4	10.1	7.6	7.3	10.2	8.2	7.2	9.2	6.9	5.6	7.6
6	9.1	9.7	8.2	9.9	7.8	6.5	8.2	7.5	N.S.T.[b]	N.S.T.
8	9.6	6.5	8.6	9.4	7.2	5.6	8.6	6.6	4.2	6.6
12	7.7	7.7	6.9	7.7	6.9	4.6	7.3	5.7	4.0	5.5
24	5.8	4.8	4.0	5.4	5.2	3.2	6.4	4.9	3.2	4.4
48	3.3	2.7	2.6	3.7	2.6	1.6	3.1	1.5	N.S.T.	N.S.T.
Percent of dose in 0–24-hr urine as intact drug	0.2	0.2	0.5	0.2	0.2	0.2	0.3	0.5	0.2	0.3
Area under blood level curve[c], ng/ml/hr	297	259	229	299	249	181	297	230	162	213
Blood peak time, hr	1–1.5	1.5	8	2	4	2	1.5	1	2.0	1.5–4.0
Blood peak concentration, ng/ml	10.7	13.0	8.6	12.6	8.2	10.9	12.6	13.5	6.5	7.6
Apparent first-order elimination rate constant, hr^{-1}	0.025	0.030	0.029	0.024	0.026	0.033	0.024	0.037	0.018	0.027
Corresponding half-life, hr	27.7	23.1	23.9	28.9	26.6	21.0	28.9	18.7	39.0	25.9

[a] N.M. = not measurable, <0.5 ng/ml using a 2-ml specimen per analysis. [b] N.S.T. = no specimen taken. [c] Calculated using trapezoidal rule.

EXPERIMENTAL

Clonazepam—Clonazepam exhibits pKa values of 1.5 and 10.5. The pKa of 1.5 corresponds to the removal of the proton of the protonated nitrogen in the 4-position of the molecule, and the pKa of 10.5 corresponds to the deprotonation of the nitrogen in the 1-position. Therefore, the compound would be virtually undissociated throughout the physiological pH range. It exhibits low aqueous solubility within the physiological pH range, with a maximum of 76 μg/ml at pH 2.0 and a minimum of 19 μg/ml at pH 7.4. The permeability characteristics of clonazepam across the everted rat intestinal sac are consistent with good absorbability (16). This suggests that once in solution the permeability (absorbability) of clonazepam across the GI mucosa will not be a rate-limiting factor following oral administration of the drug.

Clonazepam in the Dog—Clonazepam was administered to a dog intravenously and orally, on separate occasions, as a 2.3-mg/kg dose in propylene glycol solution. The same dog also received a 2.3-mg/kg dose orally as a solid, administered as the nonmicronized drug, hand packed into gelatin capsules and as the micronized drug formulated into 2-mg tablets. Five-milliliter oxalated blood specimens were obtained at appropriate time intervals up to 72 hr postdosing. The total volumes of urine voided were collected at 24-hr intervals from −24 to 72 hr following each administration. All specimens were stored frozen until analyzed.

The blood level data following intravenous and oral administrations of clonazepam in a dog are presented in Fig. 1. The pharmacokinetic profile of clonazepam in the dog is summarized in Table I. The recovery of intact drug in the 0–72-hr urine was less than 0.1% of the administered dose following intravenous administration and was nonmeasurable following oral administration. These findings suggest complete biotransformation and/or alternative routes of excretion.

Following the intravenous administration of clonazepam, a

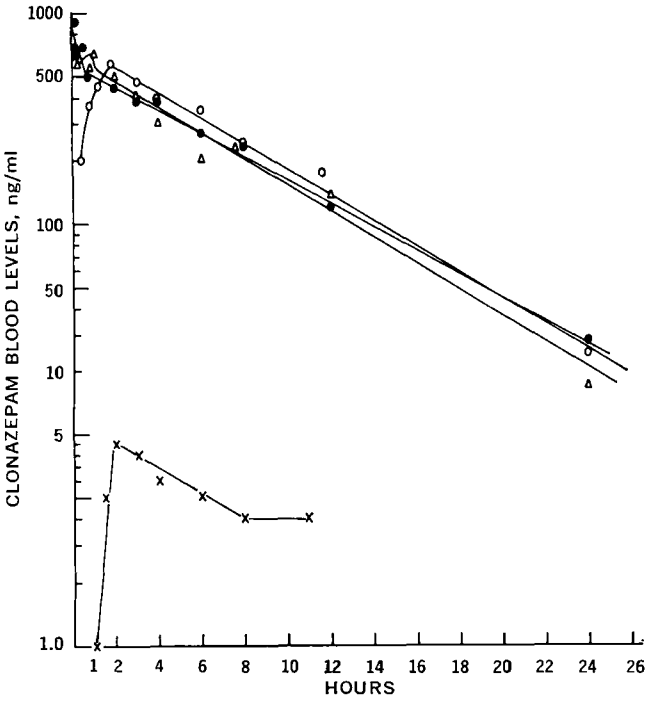


Figure 1—*Clonazepam blood level curves in a dog following intravenous and oral administration of 2.3-mg/kg doses. Key: ●, intravenous solution; △, oral solution; X, oral solid (non-micronized in gelatin capsule); and ○, oral solid (micronized in tablet formulation).*

biexponential blood level curve was observed (Fig. 1). Therefore, the pharmacokinetic evaluation of clonazepam would require a minimum of a two-compartment open-system model as previously described (17).

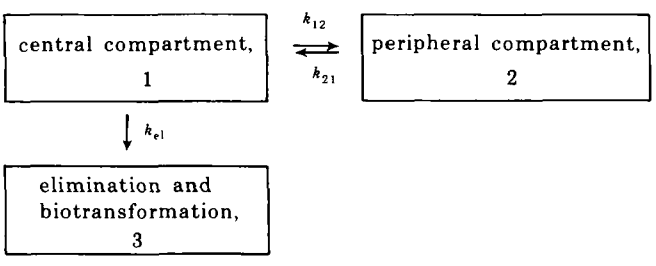
The first exponential is referred to as the fast disposition rate, with a rate constant α, and reflects the disposition of the compound from the central compartment into the body tissues. The second exponential is referred to as the slow disposition rate or "apparent" elimination rate, with a rate constant β. Both α and β are hybrid first-order rate constants which are each influenced by all of the individual processes involved in the disposition of the drug.

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

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

where $(C_p)_t$ is the concentration of drug in the blood at time t, and A and B are the ordinate axis intercepts. The individual rate constants of the model, k_{12}, k_{21}, and k_{el}, are calculable from α and β (17).

The pharmacokinetic profile of clonazepam (Table I) indicates that the initial distribution phase, α value, is rapid. The percent volume of the central compartment was calculated to be 127% of body weight, and the corresponding overall percent volume of distribution was calculated to be 224% of body weight. The drug was eliminated at a moderately rapid rate, β value of 0.129 hr^{-1}, corresponding to a half-life of 5.4 hr.



Scheme I

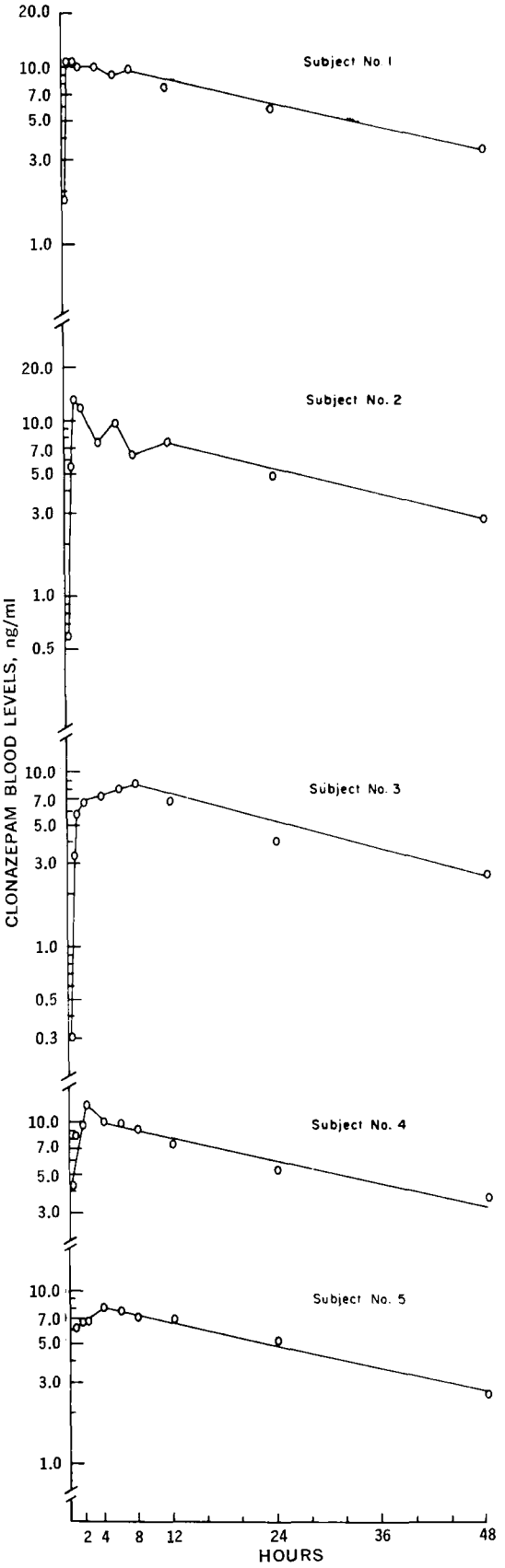


Figure 2—*Clonazepam blood level curves in humans following the administration of a single, oral 2-mg dose of the micronized drug formulated as a tablet.*

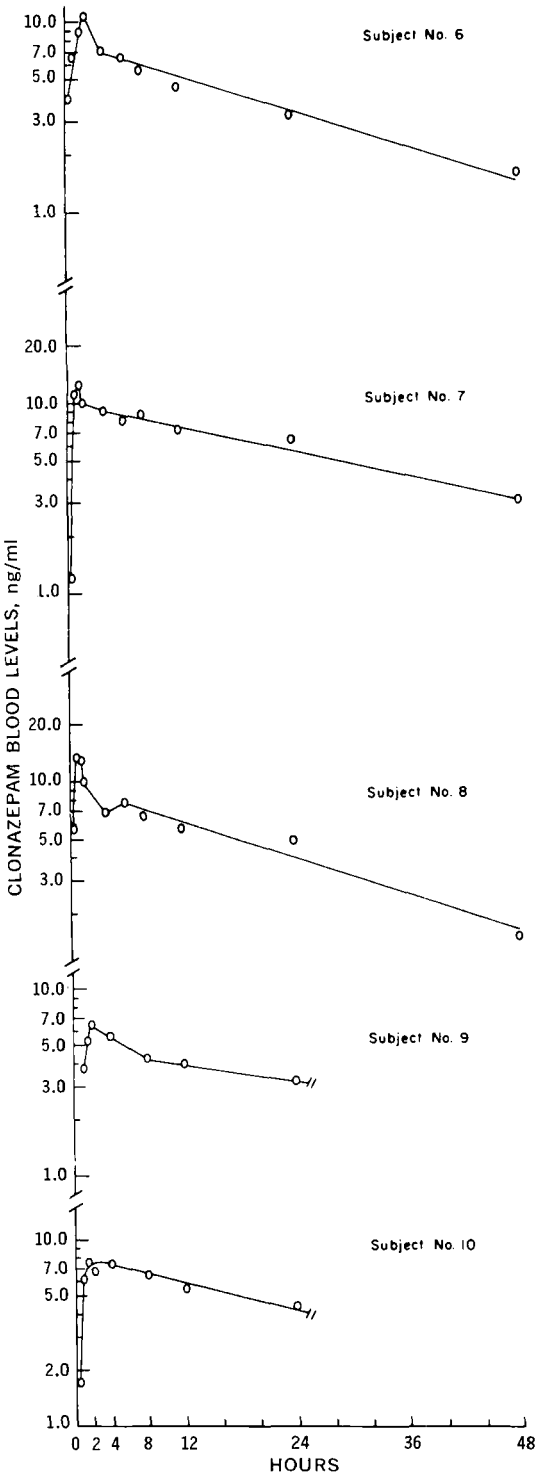


Figure 3—*Clonazepam blood level curves in humans following the administration of a single, oral 2-mg dose of the micronized drug formulated as a tablet.*

The blood level curves seen following a single oral dose of the nonmicronized drug in a gelatin capsule indicated that the absorption was slow and incomplete, with approximately 1.2% being absorbed (Fig. 1). A solution of clonazepam was prepared in propylene glycol and administered orally to circumvent the potential limitation of absorption by the dissolution rate. The blood levels showed that clonazepam administered orally in solution was absorbed rapidly and completely. The data suggest that the absorption of clonazepam can be dissolution rate limited; however, once in solution, the permeability of the drug is consistent with good absorbability. The administration of micronized clonazepam formulated as a 2-mg tablet resulted in blood levels that indicated that the micronized drug was rapidly and completely absorbed. Therefore, micronization of clonazepam succeeded in overcoming the dissolution rate-limiting characteristics of the compound in the overall absorption of the drug. Such a formulation was used in the clinical evaluation of the drug in humans.

Table III—Pharmacokinetic Parameters Associated with the Physiological Disposition of Flunitrazepam and Its *N*-Desmethyl Metabolite in the Dog

	Dog 1		Dog 2	
	Intravenous	Oral	Intravenous	Oral
Flunitrazepam Profile				
Dose, mg/kg	2	2	2	2
A, μg/ml	1.87	—	0.93	—
B, μg/ml	0.35	—	0.57	—
α, hr^{-1}	17.25	—	32.85	—
β, hr^{-1}	0.97	—	1.78	—
$t_{1/2}$, $\left(\frac{0.693}{\beta}\right)$, min	42.8	—	23.4	—
C_p^0, μg/ml	2.22	—	1.49	—
V_p, liters	11.7	—	13.4	—
% V_p, volume central compartment, % of body weight	90	—	134	—
% V_d, volume of distribution, % of body weight	345	—	242	—
k_{12}, hr^{-1}	9.96	—	13.53	—
k_{21}, hr^{-1}	3.52	—	16.78	—
k_{el}, hr^{-1}	4.73	—	4.32	—
Area under blood level curve, μg/ml/hr	0.43	0.03	0.36	—[a]
***N*-Desmethyl-Flunitrazepam Profile**				
Area under blood level curve, μg/ml/hr	4.55	2.37	3.10	1.25
Ratio of areas, oral/intravenous × 100	—	52	—	40
β, hr^{-1}	0.15	0.17	0.12	0.05
$t_{1/2}$, $\left(\frac{0.693}{\beta}\right)$, hr	4.7	4.1	6.0	13.1
Peak height, μg/ml	1.28	0.33	0.74	0.16
Peak time	5 min	4 hr	10 min	2 hr

[a] Flunitrazepam below detectable level.

Clonazepam in Humans—A clinical study was conducted with 10 adult male volunteers[1]. Each subject received a single oral 2-mg dose of micronized drug in the form of a tablet formulation in the morning following an overnight fast. Ten-milliliter oxalated blood specimens were obtained at 0 hr (control) and at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, and 48 hr after administration. The total volumes of urine voided were collected from −24 to 0 hr and from 0 to 24 hr after administration. All specimens were stored frozen until analyzed.

The blood levels, urinary excretion, and pharmacokinetic profile of clonazepam in humans are summarized in Table II; the blood level curves are shown in Figs. 2 and 3.

Peak blood levels of clonazepam were seen in eight subjects between 1 and 2 hr after administration and at 4 and 8 hr in the other two subjects, respectively. The peak blood levels ranged from 6.5 to 13 ng/ml, and the apparent elimination rate, β, of clonazepam ranged from 0.018 to 0.037 hr^{-1}. The corresponding half-lives of elimination ranged from 18.7 to 39.0 hr, with a mean of 26.4 hr. Less than 0.5% of the dose was recovered in the urine as intact drug in the 0–24-hr excretion period, indicating extensive biotransformation and/or alternative routes of excretion.

The pharmacokinetic profile of clonazepam in the dog and in humans shows that the half-life of clonazepam in the dog is four to five times shorter than in humans. In addition, both species

[1] Conducted at the Deer Lodge Research Unit, Deer Lodge, Mont., under the supervision of Dr. J. D. Moore.

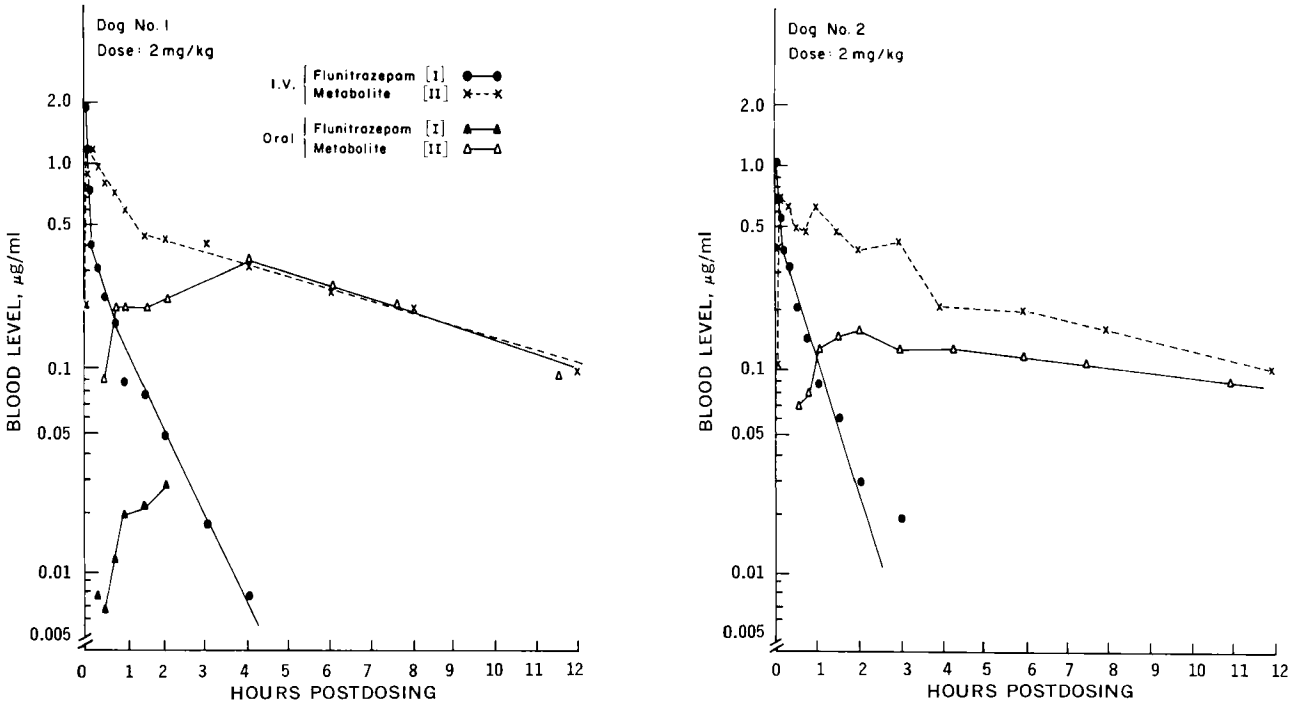


Figure 4—*Blood level curves of flunitrazepam [I] and its* N*-desmethyl metabolite [II] in two dogs following the intravenous and oral administration of 2-mg/kg doses of the drug.*

show extensive biotransformation of clonazepam, with less than 0.5% of the dose recovered in the urine as the intact drug. The data presented herein are consistent with the previously reported findings (10).

Pharmacokinetics of Flunitrazepam in Dog—Flunitrazepam exhibits a pKa of 1.8, which would allow the drug to be virtually unionized in the physiological pH range. The aqueous solubility decreases with an increase in pH, being 850 μg/ml at pH 1 and 11 μg/ml at pH 5.3. The permeability of the drug across the lumen of the everted rat intestinal sac (16) was consistent with good absorbability. Such *in vitro* parameters suggest a potential for a dissolution rate-limited absorption. However, once in solution the drug should transfer readily from the GI tract into the bloodstream.

In vivo studies were performed in which two dogs, Dogs 1 and 2, each received a 2-mg/kg single intravenous dose administered in propylene glycol and a single oral dose of micronized drug administered in a gelatin capsule 1 week apart. Oxalated blood specimens were obtained at appropriate time intervals up to 72 hr after administration by each route, and the entire volume of urine voided was collected at 24-hr intervals from −24 to 72 hr after administration.

Following intravenous administration of flunitrazepam in the two dogs, the biexponential blood level curves (Fig. 4) suggested that the pharmacokinetic evaluation would require minimally a two-compartment open-system model (17) as described for clonazepam in the dog. The pharmacokinetic parameters of flunitrazepam (Table III) show that the fast disposition rate constant, α, was 17.2 and 32.8 hr^{-1} for Dogs 1 and 2, respectively. These values correspond to an apparent half-life of 2.4 and 1.3 min, respectively. The slow disposition rate constants, β, of 0.97 and 1.78 hr^{-1} correspond to an apparent half-life of 43 and 23 min, respectively. The magnitude of the rate constants α and β indicates that the drug is distributed and eliminated at very rapid rates.

The volume of the central compartment, V_p, was 90 and 134% of body weight, whereas the total volume of distribution, V_d, was calculated to be 345 and 242% of body weight in Dogs 1 and 2, respectively, indicating extensive distribution of flunitrazepam in the dog.

Following the oral administration of the drug, only Dog 1 showed measurable blood levels of the parent drug, which were both low and erratic. No measurable blood levels of flunitrazepam were seen in Dog 2 following oral administration. This might be attributed to poor absorption, biodegradation in the GI tract, or rapid metabolism during the first pass of the drug through the liver. However, following both the intravenous and oral administrations of flunitrazepam, rapid biotransformation is evident from the levels of the *N*-desmethyl metabolite, the only metabolite detectable by the assay procedure (Table III and Fig. 4).

The areas under the blood level curve of the *N*-desmethyl flunitrazepam following the intravenous and oral administrations of flunitrazepam in each dog were compared. Their ratios indicate that at least 40–50% of the administered compound was available following oral administration but mostly as the *N*-desmethyl metabolite. Therefore, the lack of measurable parent drug in the blood after oral administration can probably be attributed to the GI or first-pass metabolism effect. The comparison of areas for the metabolite may lead to an underestimation of the extent of availability of administered drug if absorption is nonlinear due to the low solubility and slow dissolution rate in the GI tract. However, more extensive studies will be required to define the oral drug level profile. No measurable levels of either flunitrazepam or *N*-desmethyl-flunitrazepam were seen in the urine of both dogs, indicating complete and extensive biotransformation and/or alternative routes of excretion. The assay procedure did not allow for the detection of other possible metabolites.

SUMMARY

The pharmacokinetic profile of clonazepam in the dog indicated that the drug exhibited a volume of distribution of 224% body weight and that it was extensively biotransformed and rapidly eliminated. Less than 1% of the dose was detected in the 0–72-hr urine as intact drug, indicating complete biotransformation and/or alternative routes of excretion. The drug was rapidly and completely absorbed following oral administration.

In humans, a 2-mg single oral dose exhibited peak blood levels ranging from 6.5 to 13.5 ng/ml at 1–2 hr after administration. The apparent half-life of elimination ranged from 18.7 to 39.0 hr. Less than 0.5% of the dose was recovered in the urine as intact clonazepam, again indicating complete biotransformation and/or alternative routes of excretion.

The pharmacokinetic profile of flunitrazepam in the dog indicates that this drug exhibited a volume of distribution of approximately 300% body weight and was also extensively biotrans-

formed and rapidly eliminated. The virtually instantaneous biotransformation of flunitrazepam to its *N*-desmethyl metabolite, the major blood component seen following both intravenous and oral administrations of the drug, suggests a first-pass effect. The apparent half-life of elimination of the *N*-desmethyl metabolite following intravenous administration of flunitrazepam was 4.7 and 6 hr in the two dogs studied. No measurable levels of either flunitrazepam or *N*-desmethyl-flunitrazepam were seen in the urine, indicating extensive and complete biotransformation and possible alternative routes of excretion.

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ACKNOWLEDGMENTS AND ADDRESSES

Received July 30, 1973, from the *Department of Biochemistry and Drug Metabolism, Hoffmann-La Roche Inc., Nutley, NJ 07110*

Accepted for publication December 12, 1973.

[x] To whom inquiries should be directed.

Partition Coefficients of Fluorocarbon Aerosol Propellants in Water, Normal Saline, Cyclohexane, Chloroform, Human Plasma, and Human Blood

SARFARAZ NIAZI and WIN L. CHIOU[x]

Abstract □ Partition coefficients of the three most commonly used fluorocarbon propellants (trichloromonofluoromethane, dichlorodifluoromethane, and dichlorotetrafluoroethane) in water, normal saline, cyclohexane, chloroform, human plasma, and human blood were studied over a wide range of propellant concentrations. They were all found to be independent of concentration. No salting-out effect was seen in normal saline. The partition coefficients in plasma and blood were much greater than in normal saline. The implications of the results of this study on absorption, distribution, elimination, and assay of these propellants are discussed.

Keyphrases □ Fluorocarbon aerosol propellants—partition coefficients in six solvents □ Aerosol propellants, fluorocarbon—partition coefficients in six solvents □ Partition coefficients—determined for fluorocarbon aerosol propellants, six solvents □ Dichlorodifluoromethane—partition coefficient in six solvents □ Dichlorotetrafluoroethane—partition coefficient in six solvents □ Trichloromonofluoromethane—partition coefficient in six solvents

Solubilities of many volatile or gaseous anesthetic compounds in a liquid medium such as blood and olive oil have been often defined as being equivalent to their partition coefficients between the liquid phase and gaseous phase at an equilibrium state. The importance of this parameter to the absorption, distribution, elimination, and pharmacological activities of many compounds in humans and animals has been excellently reviewed (1). Volatile fluorocarbons such as trichloromonofluoromethane, dichlorodifluoromethane, and dichlorotetrafluoroethane have been widely used as propellants in aerosol products for cosmetic, pharmaceutical, household, and other purposes. The toxicity of these fluorocarbon propellants has been a subject of intensive research and controversy in recent years, as was clearly illustrated in an editorial (2) and a rebuttal (3) to that editorial published recently.

After inhalation in human subjects, Paterson *et al.* (4) were unable to quantify dichlorodifluoromethane and dichlorotetrafluoroethane in blood. The fast elimination from the body and loss to the air from blood samples due to their high volatility or low solubility in blood were implicated as possible causes. More recently, Morgan *et al.* (5) correlated the observed slower tracheal absorption rates in humans of dichlorodifluoromethane and dichlorotetrafluoroethane with their lower solubilities in olive oil. Although they also reported the solubilities of four fluorocarbon propellants at one concentration for