Pharmacokinetics and Bioavailability of Intravenous, Intramuscular, and Oral Lorazepam in Humans

DAVID J. GREENBLATT *x, RICHARD I. SHADER ‡, KATE FRANKE *, DEAN S. MacLAUGHLIN *, JEROLD S. HARMATZ ‡, MARCIA DIVOLL ALLEN *, ANN WERNER *, and ELAINE WOO *

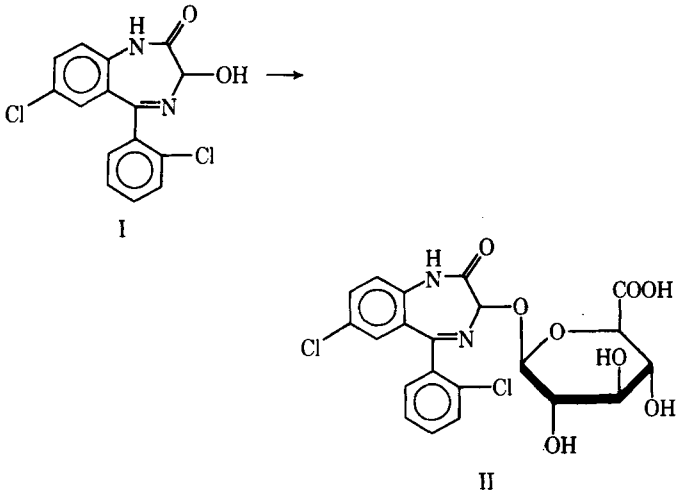
Received February 21, 1978, from the *Clinical Pharmacology Unit, Massachusetts General Hospital, Boston, MA 02114, and the ‡Psychopharmacology Research Laboratory, Massachusetts Mental Health Center, Boston, MA 02115. Accepted for publication June 8, 1978.

Abstract □ Six healthy volunteers received single 2- and 4-mg doses of lorazepam by 5-min intravenous infusion, in tablet form by mouth in the fasting state, and by deltoid intramuscular injection in a six-way crossover study. A seventh subject received the 4-mg iv, po, and im doses. Concentrations of lorazepam and its glucuronide metabolite in multiple plasma samples and in all urine collected during 72 hr after each dose were determined by electron-capture GLC. Mean kinetic variables for intravenous lorazepam after 2- and 4-mg doses, respectively, were: volume of distribution (V_d), 1.14 and 1.30 liters/kg; elimination half-life ($t_{1/2\beta}$), 14.3 and 14.6 hr; total clearance, 1.05 and 1.10 ml/min/kg; and cumulative urinary excretion of lorazepam glucuronide, 81.1 and 82.3% of the dose. With the possible exception of V_d, all kinetic variables were dose independent. Following a lag time averaging 15–17 min, absorption of oral lorazepam was first order, with apparent absorption half-life ($t_{1/2a}$) values averaging 40 (2-mg dose) and 22 (4-mg dose) min. Absorption was 91–95% complete. No lag times were observed after intramuscular injection of lorazepam; absorption was first order, with $t_{1/2a}$ values averaging 12 (2-mg dose) and 19 (4-mg dose) min. The completeness of absorption was 83–100%. Absorption kinetics for both oral and intramuscular lorazepam were dose independent. Plasma $t_{1/2\beta}$ for intact lorazepam was independent of dose and administration route.

Keyphrases □ Lorazepam—pharmacokinetics and bioavailability in humans, various administration routes compared □ Pharmacokinetics—lorazepam in humans, various administration routes compared □ Bioavailability—lorazepam in humans, various administration routes compared □ Benzodiazepines—lorazepam, pharmacokinetics and bioavailability in humans, various administration routes compared

Lorazepam (I, Scheme I), a 3-hydroxy-1,4-benzodiazepine derivative, is extensively used as a sedative and antianxiety agent (1, 2). Previous studies (3–8) investigated the disposition of lorazepam in humans following intravenous, intramuscular, and oral administration to different groups of subjects. However, the effect of dose on lorazepam pharmacokinetics and the absolute bioavailability of extravascular modes of administration are not established.

The present study assessed the pharmacokinetics of intravenous lorazepam at two doses within the usual therapeutic range. Also assessed were the rate and completeness of absorption of oral and intramuscular lorazepam in the same subjects at two different dosage levels.



Scheme I

EXPERIMENTAL

Subjects—The seven healthy male and female volunteers[1] (Table I) ranged in age from 23 to 31 years and were within 10% of ideal body weight. All subjects had normal hematologic profiles and laboratory screening tests[2] and had no identifiable medical disease. They had no history of current or chronic psychotropic drug use.

Procedure—The first six subjects received single doses (2 or 4 mg iv, po, or im) of lorazepam on six occasions separated by at least 1 week. The seventh subject (EM) terminated participation after four trials; only data from the three 4-mg trials are included in the analysis. Table I shows the sequence of drug administration for each subject.

For intravenous administration, 1 ml of injectable lorazepam solution, containing 2 or 4 mg dissolved in its customary solvent[3], was diluted to 50 ml with 5% dextrose in water. The dose was infused into an antecubital vein over 5 min using a constant-rate infusion pump. For intramuscular administration, 1 ml of injectable lorazepam, containing 2 or 4 mg, was administered as a single deltoid injection. Oral lorazepam was administered as one or two 2-mg tablets together with 100 ml of water following an overnight fast.

Venous blood samples were drawn from an indwelling scalp vein cannula or by separate venipuncture at the following times after the termination of the intravenous infusion or the oral and intramuscular doses: 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3, 4, 6, 8, 12, 18, 24, 30, 36, and 48 hr. Following intravenous administration, additional samples were drawn just at the termination of the infusion and at 2 and 5 min postinfusion. All blood specimens were collected in heparinized vacuum tubes.

All urine was collected for 72 hr after each dose in intervals divided as follows: 0–4, 4–8, 8–24, 24–48, and 48–72 hr.

Plasma samples and aliquots of all urine collections were stored at −20° until assayed.

Analysis of Plasma and Urine—Concentrations of intact lorazepam in 1-ml samples of plasma and urine were determined by electron-capture GLC as described elsewhere (9). Urinary concentrations of lorazepam glucuronide (II, Scheme I), the major human metabolite of lorazepam, were likewise determined after enzymatic deconjugation with β-glucuronidase. Oxazepam served as the internal standard for all analyses, and the two compounds were chromatographed without prior derivatization. The sensitivity of the method was 1–3 ng of lorazepam/ml of original sample. The variation of identical samples did not exceed 5%.

Data Analysis—Postinfusion plasma lorazepam concentrations were analyzed by weighted iterative nonlinear least-squares regression analysis (10, 11). The iterative process was allowed to proceed until the convergence criteria were met or a total of 50 iterative steps was completed. Since concentration values generally spanned two log scales, each residual error, prior to squaring, was weighted by a factor equal to the reciprocal

[1] Written informed consent was obtained.
[2] SMA-20.
[3] Containing 0.02 ml of benzyl alcohol and 0.18 ml of polyethylene glycol; volume adjusted to 1.0 ml with propylene glycol.

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Table I—Characteristics of Subjects and Sequence of Lorazepam Administrations

Subject	Age, years	Sex	Weight, kg	Sequence of Trials (Dose and Route)					
				1[a]	2	3	4	5	6
JH	30	F	53.6	2 im	4 po	2 iv	4 im	2 po	4 iv
JK	26	M	76.4	2 im	4 iv	2 po	4 im	2 iv	4 po
HJP	25	M	79.5	2 po	4 iv	2 im	4 im	4 po	2 iv
DJG	31	M	69.5	2 im	4 iv	2 po	4 im	2 iv	4 po
EO	29	F	65.9	2 po	4 iv	2 im	4 po	4 im	2 iv
LW	27	F	53.6	2 po	4 im	2 im	4 po	4 iv	2 iv
EM[b]	23	F	56.8	2 iv	4 po	4 im	4 iv		

[a] Trial number. [b] This subject withdrew from the study after four trials; findings from the 2-mg iv trial were not included in the analysis.

Table II—Pharmacokinetics of Intravenous Lorazepam[a]

Subject	V_1, liters/kg	V_d, liters/kg	$t_{1/2\alpha}$, min	$t_{1/2\beta}$, hr	Clearance, ml/min/kg	$AUC_{0\rightarrow\infty}$, ng/ml × hr	72-hr Excretion of Lorazepam as Glucuronide, % of dose	Half-Life Determined from Lorazepam Glucuronide Excretion Rate *versus* Time, hr	Projected Cumulative Excretion of Lorazepam as Glucuronide, % of dose
					Dose = 2 mg				
JH[b]	0.30	1.30	1.4	12.4	1.22	511.7	64.9	14.1	66.9
JK	0.12	1.13	1.9	8.4	1.56	279.7	82.1	11.0	83.3
HJP	0.48	1.05	10.4	9.9	1.23	341.1	87.7	16.6	93.1
DJG	0.28	1.11	1.1	24.9	0.52	924.4	63.2	23.4	72.9
EO	—[c]	1.16	0.0	12.8	1.04	485.6	91.0	16.8	96.1
LW	0.36	1.14	1.3	17.6	0.74	836.0	67.5	19.5	74.2
Mean	0.30	1.14	2.7	14.3	1.05	563.1	76.1	16.9	81.1
±*SE*	±0.05	±0.03	±1.6	±2.5	±0.15	±107.0	±5.0	±1.7	±4.8
					Dose = 4 mg				
JH	0.94	1.43	18.9	14.0	1.18	1053.8	81.5	14.8	85.0
JK[d]	0.51	1.25	2.0	12.6	1.15	760.4	78.7	12.2	80.2
HJP	0.40	1.10	0.9	12.6	1.01	828.4	88.2	14.6	91.8
DJG	1.15	1.24	12.0	22.0	0.65	1468.4	49.4	24.6	58.1
EO	0.32	1.30	2.1	12.3	1.22	830.5	92.0	14.2	95.2
LW	0.66	1.21	27.9	18.0	0.78	1600.2	66.0	14.5	70.0
EM	1.10	1.62	5.1	10.6	1.77	664.3	94.6	10.4	95.7
Mean	0.72	1.30	9.8	14.6	1.10	1029.4	78.6	15.1	82.3
±*SE*	±0.12	±0.06	±3.9	±1.5	±0.13	±138.4	±6.1	±1.7	±5.3

[a] See text for explanation of abbreviations. [b] Intermediate pi half-life of 0.49 hr following 2-mg dose. [c] Indeterminant V_1 due to large value of alpha. [d] Intermediate pi half-life of 0.37 hr following 4-mg dose.

Table III—Pharmacokinetics of Oral Lorazepam[a]

Subject	Lag Time, min	Peak Concentration, ng/ml	Time of Peak Concentration, hr after dose	$t_{1/2a}$, min	$t_{1/2\beta}$, hr	Half-Life Determined from Lorazepam Glucuronide Excretion Rate *versus* Time, hr
			Dose = 2 mg			
JH	0	36.2	1.0	56.9	15.2	13.4
JK	5.9	21.5	2.5	50.2	9.3	13.6
HJP	16.2	23.3	2.0	26.0	9.0	13.4
DJG	—[b]	26.0	6.0	—[b]	25.9	38.3
EO	12.5	27.3	2.0	60.2	18.6	12.8
LW	41.5	31.5	1.5	8.5	19.3	16.2
Mean	15.2	27.6	2.50	40.4	16.2	18.0
±*SE*	±7.1	±2.2	±0.73	±10.0	±2.6	±4.1
			Dose = 4 mg			
JH	14.4	45.1	1.0	1.0	16.7	15.2
JK	0	47.5	1.5	44.1	14.0	12.8
HJP	24.5	47.8	2.5	17.3	11.1	14.8
DJG	26.5	38.8	1.5	17.3	25.0	31.4
EO	42.8	44.2	1.5	30.3	15.5	12.6
LW	0	68.1	2.0	30.8	15.9	14.9
EM	11.3	44.4	1.0	14.3	10.8	12.3
Mean	17.1	48.0	1.57	22.1	15.6	16.3
±*SE*	±5.8	±3.5	±0.20	±5.3	±1.8	±2.6

[a] See text for explanation of abbreviations. [b] Absorption pattern not consistent with a first-order process.

of that plasma concentration. Data points were fitted to the following function:

$$C = Ae^{-\alpha t} + Be^{-\beta t} \quad \text{(Eq. 1)}$$

where C is the plasma lorazepam concentration at time t after the end of the infusion; A and B are hybrid intercept terms that were subsequently corrected for the infusion period (12); and α and β are hybrid exponents, representing apparent phases of drug distribution and elimination, respectively (6–8, 13–16). For two of the 13 subject trials, Eq. 1 did not explain the data adequately. Accordingly, the points were fitted to an equation of the following form:

$$C = Ae^{-\alpha t} + Pe^{-\pi t} + Be^{-\beta t} \quad \text{(Eq. 2)}$$

Use of this equation in these two cases considerably improved the quality of the fit and substantially reduced the residual error.

Coefficients and exponents from the fitted function were used to calculate the following pharmacokinetic variables: volume of the central compartment (V_1), total apparent volume of distribution using the "area"

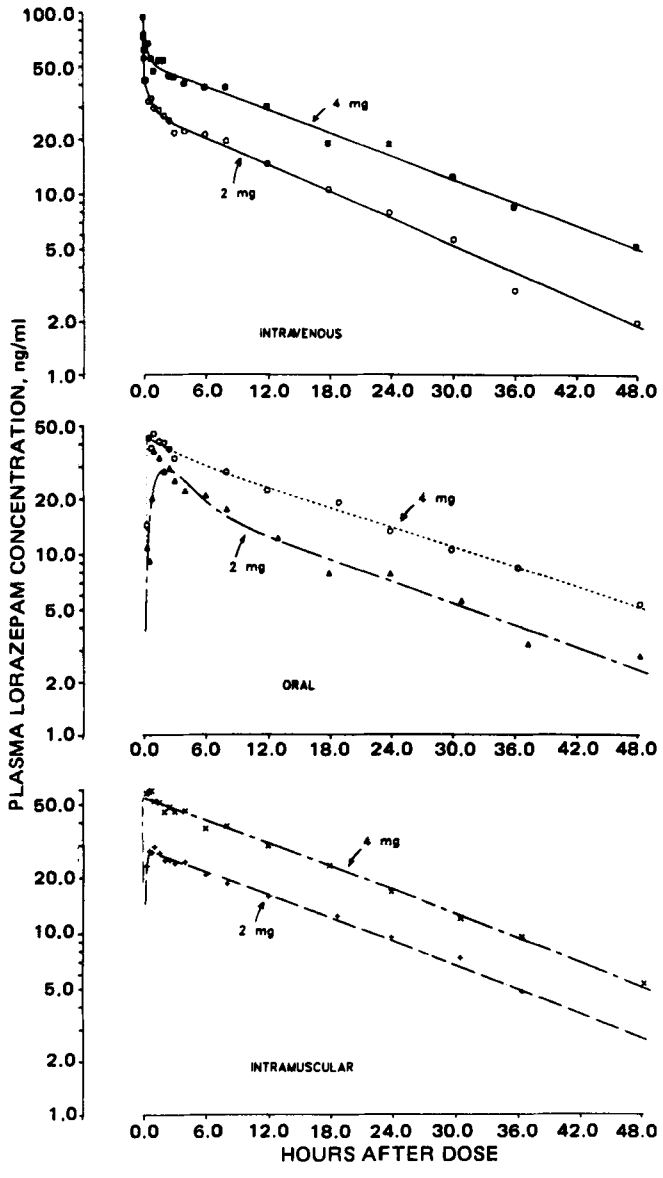

Figure 1—*Plasma lorazepam concentrations and pharmacokinetic functions for Subject JH.*

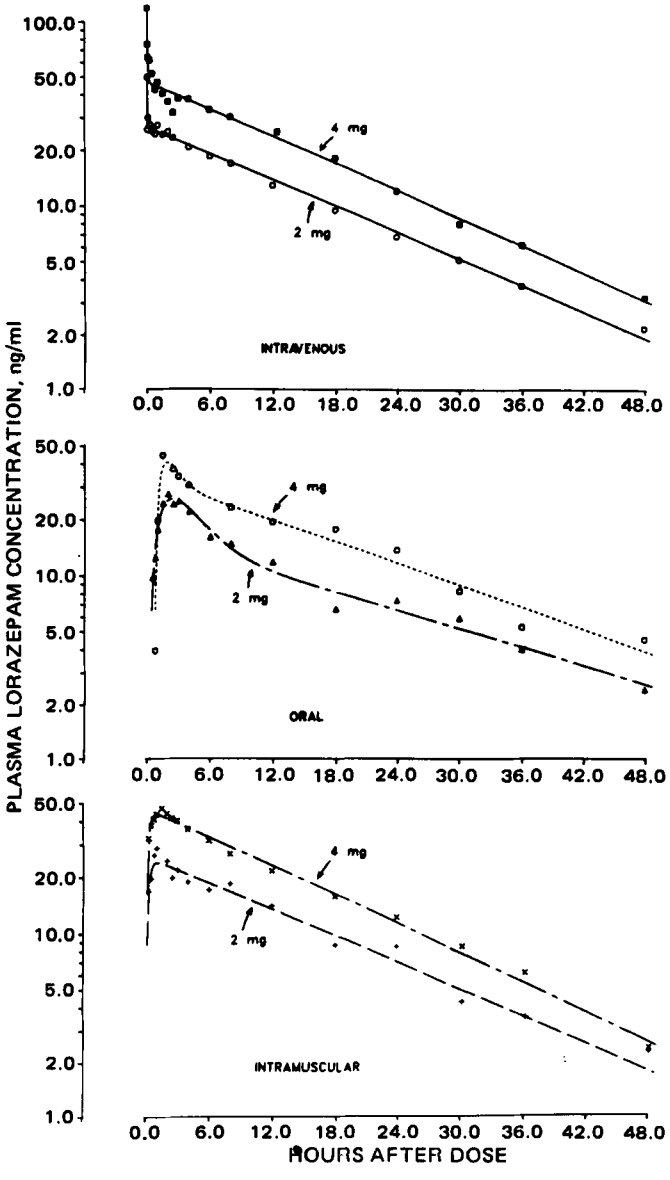

Figure 2—*Plasma lorazepam concentrations and pharmacokinetic functions for Subject EO.*

method (V_d), apparent distribution half-life ($t_{1/2\alpha}$), apparent elimination half-life ($t_{1/2\beta}$), and total clearance (6–8, 13–16). When appropriate, an intermediate "pi" half-life ($t_{1/2\pi}$) also was calculated. Individual "micro" transfer and elimination rate constants corresponding to the two- or three-compartment open pharmacokinetic models were not determined since these constants are dependent on the ambiguous configuration of compartments within the model (17, 18). The micro rate constants can be calculated using the data presented under *Results*.

The half-life also was determined from the slope of the terminal log-linear portion of a plot of the average urinary excretion rate (interval excretion divided by interval length) *versus* the midpoint of the collection interval. The amount of lorazepam glucuronide remaining to be excreted between 72 hr and "infinity" was determined as the quotient of the projected excretion rate at 72 hr and the apparent urinary excretion rate constant. This quantity was added to the 72-hr cumulative excretion to give the cumulative excretion of lorazepam glucuronide from time zero to infinity.

Plasma lorazepam concentrations following extravascular modes of administration were analyzed by similar methods. Since concentration values generally spanned one log scale, the weighting factor for each residual error prior to squaring was the reciprocal of the square root of the plasma concentration. Data points were fitted to each of the following two functions:

$$C = A(e^{-\beta t} - e^{-k_a t}) \qquad \text{(Eq. 3)}$$

$$C = -(A + B)e^{-k_a t} + Ae^{-\alpha t} + Be^{-\beta t} \qquad \text{(Eq. 4)}$$

As in Eqs. 1 and 2, C is the plasma lorazepam concentration at time t after the dosage; A and B are hybrid intercept terms; α and β are hybrid exponents; and k_a is the apparent first-order absorption rate constant, which was used to calculate the apparent first-order absorption half-life ($t_{1/2a}$). The constant k_a serves as only an apparent rate constant and does not necessarily correspond to a microconstant associated with any particular pharmacokinetic model (15–18).

In all subject trials, the choice between Eqs. 3 and 4 as function of best fit was determined by assessment of the randomness of scatter of actual data points about the fitted function and by comparison of the sum of squares of weighted residual errors (19). In most subject trials following oral lorazepam administration, Eqs. 3 and 4 required further modification by introduction of a lag time (t_0), which elapsed prior to the start of absorption.

The apparent systemic availability of oral and intramuscular lorazepam was determined using the following three variables: (*a*) the total area under the plasma lorazepam concentration–time curve from time zero to infinity ($AUC_{0\to\infty}$), calculated using the appropriate pharmacokinetic

Table IV—Pharmacokinetics of Intramuscular Lorazepam [a]

Subject	Peak Concentration, ng/ml	Time of Peak Concentration, hr after dose	$t_{1/2\alpha}$, min	$t_{1/2\beta}$, hr	Half-Life Determined from Lorazepam Glucuronide Excretion Rate *versus* Time, hr
			Dose = 2 mg		
JH	29.0	1.0	5.4	14.3	13.0
JK	26.7	2.0	11.4	15.8	11.3
HJP	23.3	1.0	15.0	11.6	14.5
DJG	24.3	1.5	18.6	23.3	31.7
EO	28.2	1.0	9.6	12.6	15.7
LW	29.4	0.75	12.6	16.8	16.0
Mean	26.8	1.20	12.1	15.7	17.0
±*SE*	±1.0	±0.18	±1.8	±1.7	±3.0
			Dose = 4 mg		
JH	58.6	0.75	~0	14.1	13.7
JK	62.9	1.0	28.2	12.4	13.5
HJP	34.3	0.75	10.8	10.5	14.6
DJG	42.0	0.75	17.4	25.6	26.5
EO	46.3	1.5	9.0	11.5	13.5
LW	51.9	1.0	16.8	24.7	18.9
EM	36.2	2.5	50.6	13.9	12.3
Mean	47.5	1.17	19.0	16.1	16.1
±*SE*	±4.1	±0.24	±6.2	±2.4	±1.9

[a] See text for explanation of abbreviations.

Table V—Bioavailability of Oral Lorazepam

Subject	$AUC_{0\to\infty}$ ng/ml × hr	$AUC_{0\to\infty}$ % of iv value	72-hr Excretion of Lorazepam as Glucuronide % of dose	72-hr Excretion of Lorazepam as Glucuronide % of iv value	Projected Cumulative Excretion of Lorazepam as Glucuronide % of dose	Projected Cumulative Excretion of Lorazepam as Glucuronide % of iv value
			Dose = 2 mg			
JH	491.6	96.1	86.2	132.8	88.2	131.8
JK	307.4	109.9	50.9	62.0	52.5	63.0
HJP	317.9	93.2	62.1	70.8	64.1	68.9
DJG	905.7	98.0	59.2	93.7	82.4	113.0
EO	467.1	96.2	82.4	90.5	84.5	87.9
LW	537.7	64.3	56.6	83.9	59.9	80.6
Mean	504.6	92.9	66.2	88.9	71.9	90.9
±*SE*	±88.9	±6.2	±5.9	±10.1	±6.1	±10.9
			Dose = 4 mg			
JH	898.3	85.2	76.4	93.7	80.5	94.7
JK	664.4	87.4	101.2	128.6	104.1	129.8
HJP	782.2	94.4	62.1	70.4	65.9	71.8
DJG	1405.3	95.7	44.3	89.7	57.2	98.4
EO	737.2	88.8	83.7	91.0	85.7	90.0
LW	1496.4	93.5	60.6	91.8	63.4	90.5
EM	691.7	104.1	82.4	87.1	84.1	87.9
Mean	953.6	92.7	73.0	93.2	77.3	94.7
±*SE*	±131.8	±2.4	±7.1	±6.6	±6.1	±6.6

function; (*b*) the 72-hr urinary excretion of lorazepam glucuronide; and (*c*) the projected cumulative excretion of lorazepam glucuronide (13–16, 20). Each variable was compared to the corresponding value following intravenous administration of the same dose to the same subject.

Statistical methods included analysis of variance and the Student *t* test (21).

RESULTS

Intravenous Lorazepam—*Subjective Effects*—Subjective central nervous system (CNS) effects appeared rapidly after the intravenous infusion and included drowsiness, ataxia, dysarthria, and loss of recall. These effects abated gradually between 2 and 12 hr after dosage and had essentially disappeared 24 hr after dosage. No serious untoward consequences were encountered. The effects of the 2-mg dose were qualitatively similar but less intense and of shorter duration than those of the 4-mg dose.

Pharmacokinetics—Disappearance of lorazepam from plasma was consistent with Eq. 1 in 11 subject trials and with Eq. 2 in the other two (Table II). The initial distribution phase proceeded rapidly, with distribution half-life values of less than 20 min in all but one subject trial. The apparent elimination half-life averaged 14–15 hr, and the total clearance averaged about 1.1 ml/min/kg. Mean total apparent volumes of distribution were slightly larger than body weight.

The 72-hr urinary excretion of intact lorazepam did not exceed 0.5% of the dose in any subject. In contrast, a mean of 76–79% of the dose was excreted as lorazepam glucuronide in 72 hr; the projected cumulative excretion of lorazepam glucuronide averaged more than 80% of the dose. The half-life determined from the lorazepam glucuronide excretion rate *versus* time data averaged 15–17 hr and was highly correlated with the apparent plasma elimination half-life of intact lorazepam for both the 4- ($r = 0.89$) and 2- ($r = 0.91$) mg doses.

Based on the six subjects who received both doses of intravenous lorazepam, there was no significant difference between the two dosage levels in V_1 (paired $t = 0.97$), $t_{1/2_\alpha}$ ($t = 1.49$), $t_{1/2\beta}$ ($t = 0.89$), clearance ($t = 0.58$), 72-hr and projected cumulative excretion of lorazepam glucuronide ($t = 0.02$ and 0.23), and apparent excretion half-life of lorazepam glucuronide ($t = 1.04$). The apparent volume of distribution (V_d) after the 4-mg dose was significantly larger ($t = 7.01$) than after the 2-mg dose, but the actual difference between the two mean values was small. Figures 1 and 2 illustrate representative plasma lorazepam concentration–time curves.

Oral Lorazepam—*Subjective Effects*—Subjective CNS effects appeared within 2 hr of dosage and generally were maximal between 1 and 4 hr after dosage, after which they gradually abated. Again, the intensity and duration of clinical manifestations were greater with the 4- than with the 2-mg dose.

Pharmacokinetics—In 10 of the 13 subject trials, a lag time of 6–43

Table VI—Bioavailability of Intramuscular Lorazepam

Subject	$AUC_{0\to\infty}$ ng/ml × hr	$AUC_{0\to\infty}$ % of iv value	72-hr Excretion of Lorazepam as Glucuronide % of dose	72-hr Excretion of Lorazepam as Glucuronide % of iv value	Projected Cumulative Excretion of Lorazepam as Glucuronide % of dose	Projected Cumulative Excretion of Lorazepam as Glucuronide % of iv value
			Dose = 2 mg			
JH	573.3	112.0	70.1	108.0	72.0	107.5
JK	404.0	144.4	56.3	68.6	57.1	68.6
HJP	410.0	120.2	82.2	93.7	85.7	92.0
DJG	840.5	90.9	63.6	100.1	82.7	113.5
EO	454.4	93.6	77.4	85.1	81.3	84.6
LW	717.3	85.8	56.8	84.1	61.6	83.0
Mean	556.5	107.8	67.7	90.0	73.4	91.5
±*SE*	±73.3	±9.1	±4.4	±5.7	±4.9	±6.8
			Dose = 4 mg			
JH	1096.1	104.0	79.0	96.9	83.2	97.9
JK	756.9	99.5	52.4	66.6	53.7	66.9
HJP	547.1	66.0	73.1	82.9	76.1	82.9
DJG	1476.9	100.6	46.5	93.9	56.2	96.7
EO	757.1	91.2	77.4	83.9	79.9	83.9
LW	1413.2	88.3	54.8	83.0	59.7	85.3
EM	620.6	93.4	72.2	76.3	73.8	77.1
Mean	952.6	91.9	65.1	83.4	68.9	84.4
±*SE*	±143.0	±4.8	±5.1	±3.9	±4.6	±4.1

min elapsed prior to the start of absorption (Table III). With the exception of Subject DJG following the 2-mg dose, absorption proceeded as an apparent first-order process, with absorption half-life values ranging from 8 to 60 min. In all but one case, peak lorazepam concentrations were reached within 2.5 hr after the dosage.

There was a trend toward less rapid absorption of the 2- than of the 4-mg dose. However, based on the six subjects who received both doses, differences between doses in time of peak concentration (t = 1.08) and in apparent absorption half-life (t = 0.66) did not reach significance. The apparent plasma elimination half-life of lorazepam and the half-life determined from lorazepam glucuronide rate *versus* time data were nearly identical between the two doses (t = 0.11 and 0.78, respectively). Representative plasma concentration curves are shown in Figs. 1 and 2.

Intramuscular Lorazepam—*Subjective Effects*—Mild to moderate local discomfort associated with both intramuscular injections was reported by three of the seven subjects. The discomfort spontaneously resolved after the injection. In no case was severe pain described, nor were there any residual local complications. The onset of subjective effects was rapid, generally within 1 hr of the injection.

Pharmacokinetics—Absorption of intramuscular lorazepam proceeded as a first-order process, with no apparent lag time, in all subjects (Table IV). The mean apparent absorption half-life averaged less than 20 min after both doses, and the peak concentration was reached an average of 1.2 hr after injection (Figs. 1 and 2). There was no significant difference between the two dose levels either in the apparent absorption half-life (t = 0.48) or in the time of peak concentration (t = 1.07).

The apparent plasma elimination half-life of lorazepam and the half-life determined from the lorazepam glucoronide excretion rate *versus* time data were similar to those observed following intravenous and oral dosage. Again, there was no significant difference between the two dose levels (t = 0.45 and 0.20, respectively).

Bioavailability—Tables V and VI show the apparent systemic availability of oral and intramuscular lorazepam at both dose levels using all three measures of bioavailability. Systemic availability of the 2-mg oral dose by all three measures averaged 89–93% of the intravenous value. The availability of the 4-mg oral dose averaged 93–95%. The bioavailability of the 2-mg im dose of lorazepam averaged 90–100%, while that of the 4-mg im dose averaged 84–92% (Fig. 3).

A two-way analysis of variance was used to assess differences among the three routes of administration in the three measures of systemic availability (Table VII). For the 2-mg dose, none of the differences approached significance. Differences were of borderline significance for the 4-mg dose.

Effect of Route on Lorazepam Elimination—The effect of route of administration on the apparent elimination half-life of intact lorazepam from plasma and on the half-life determined from lorazepam glucuronide excretion rate was assessed at both dose levels using a two-way analysis of variance (Table VIII). The route of administration had no significant influence on either of these variables at either dose level (see also Fig. 4).

DISCUSSION

Distribution of lorazepam following intravenous infusion proceeded rapidly, with mean distribution half-life values of less than 10 min. This result is consistent with the prompt onset of clinical sedative effects following intravenous infusion observed in this and other studies (22–26). However, the present study was not designed to provide precise quantitation of the time course and intensity of CNS effects nor of the relation between subjective manifestations and pharmacokinetic variables.

The apparent volume of distribution of lorazepam on the average was slightly larger than body weight, indicating moderately extensive tissue uptake. The apparent elimination half-life averaged 14–15 hr, similar to values reported previously (4–9). Consistent with earlier studies (5–9, 27, 28), conjugation to glucuronic acid appeared to be the major route of lorazepam clearance. A mean of 76–79% of the dose was recovered in the urine as lorazepam glucuronide during the 72 hr after drug administration. The projected cumulative excretion of lorazepam glucuronide exceeded 80% of the dose. In contrast, excretion of intact lorazepam did not exceed 0.5% of the dose in any subject. The parallel pattern of elimination

Table VII—Bioavailability of Lorazepam: Two-Way Analysis of Variance among Three Routes of Administration

Bioavailability Measure	Dose = 2 mg F	Dose = 2 mg $d.f.$	Dose = 2 mg p	Dose = 4 mg F	Dose = 4 mg $d.f.$	Dose = 4 mg p
$AUC_{0\to\infty}$	1.42	2, 10	0.29	2.20	2, 12	0.15
72-hr excretion of lorazepam glucuronide	1.66	2, 10	0.24	2.92	2, 12	0.09
Projected cumulative excretion of lorazepam glucuronide	1.14	2, 10	0.36	2.72	2, 12	0.11

Table VIII—Effect of Route of Administration on Lorazepam Elimination

Variable	Dose = 2 mg F	Dose = 2 mg $d.f.$	Dose = 2 mg p	Dose = 4 mg F	Dose = 4 mg $d.f.$	Dose = 4 mg p
Plasma elimination half-life of intact lorazepam ($t_{1/2\beta}$)	0.98	2, 10	0.41	0.75	2, 12	0.49
Half-life determined from lorazepam glucuronide excretion rate *versus* time	0.15	2, 10	0.87	1.09	2, 12	0.37

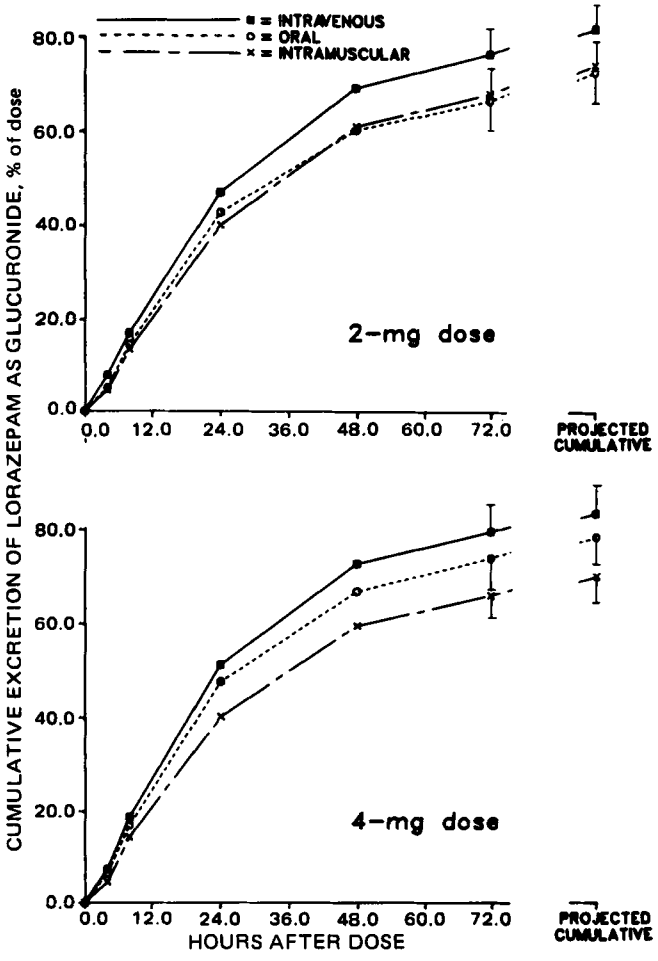

Figure 3—*Urinary excretion of lorazepam glucuronide following 2- (top) and 4- (bottom) mg doses administered by three routes. Each point is the mean (±SE when indicated) for all subjects at that point in time.*

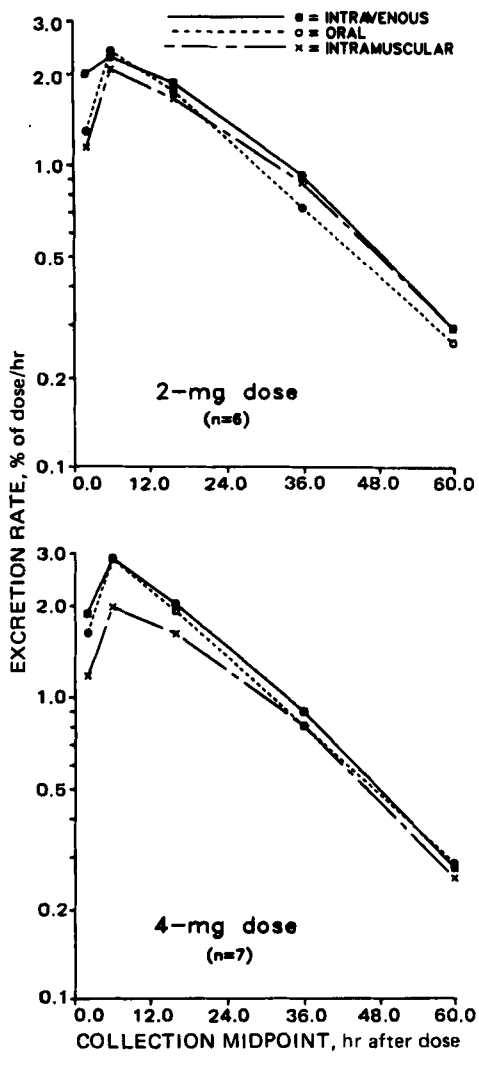

Figure 4—*Urinary excretion rate of lorazepam glucuronide following 2- (top) and 4- (bottom) mg doses administered by three routes. Each point is the mean for all subjects at that point in time. (Standard errors, omitted for clarity, are available from the authors upon request.)*

of the parent compound from plasma and of its endogenously formed metabolite in urine strongly suggests that the elimination rate of lorazepam glucuronide is determined by its formation rate rather than by its intrinsic clearance (16, 29, 30). Pharmacokinetic studies of lorazepam glucuronide administered as such would be required to determine the characteristics of clearance of this metabolic product.

With the assumptions that hepatic biotransformation accounts for essentially all of the total clearance of lorazepam and that hepatic blood flow is approximately 21 ml/kg/min in a healthy individual, the low hepatic extraction ratio of lorazepam indicates that only a fraction of an orally administered dose would fail to reach the systemic circulation due to first-pass metabolism (16, 31). Finally, none of the pharmacokinetic variables for lorazepam differed significantly between the two dose levels.

A lag time averaging 15–17 min elapsed prior to the start of absorption of oral lorazepam. Lag times were observed in previous pharmacokinetic studies of lorazepam (6) and of other benzodiazepines (32–34) and probably are attributable to the time necessary for dissolution of the oral dosage form and/or gastric emptying time. Thereafter, absorption proceeded as an apparent first-order process in all but one subject trial. There was variability between subjects and within subjects at the two dosage levels in values of apparent absorption half-life. However, there was no evidence of any systematic dose-dependent variation in absorption. In all but one subject trial, peak lorazepam levels were attained within 2.5 hr after dosage. Furthermore, the peak level attained was approximately proportional to the dose. Following attainment of peak concentrations, lorazepam elimination from plasma and apparent excretion of lorazepam glucuronide in urine proceeded at rates similar to those observed following intravenous injection of lorazepam. As reported previously with chlordiazepoxide (34, 35) and diazepam (36), the absorption of oral lorazepam appeared to be more than 90% complete.

Intramuscular injection of lorazepam did not produce excessive local discomfort. Injection site pain was described previously (23, 37, 38) but in most studies was not a clinically important problem (7, 39–47). Absorption of intramuscular lorazepam was consistently rapid, and in no case did a lag time elapse prior to the start of absorption. Peak concentrations were reached within 2.5 hr of the dosage in all subjects, and values of the apparent first-order absorption half-life averaged less than 20 min at both dosage levels. As with oral lorazepam, the peak concentration was approximately proportional to the dose. The pattern of elimination of lorazepam and the excretion of lorazepam glucuronide were very similar to those observed following intravenous and oral dosage. On the average, absorption of intramuscular lorazepam was 83–100% complete. The pharmacokinetics of intramuscular lorazepam contrast sharply with findings with intramuscular chlordiazepoxide (34, 35, 48) and diazepam (49–53). Absorption of the latter two benzodiazepine derivatives is slow and erratic and can produce unreliable clinical effects (49, 51–55). Furthermore, injection of chlordiazepoxide and diazepam is associated with considerable pain (56). The absorption profile of intramuscular lorazepam suggests that this compound may have benefits over existing benzodiazepine derivatives in some clinical situations.

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