plasma curves and cumulative excretion in the present study were poor. Correlation coefficients between AUC^{24} and Au^{48} (48-hr urinary excretion), and between C_{max} and Au^{48} for all subjects were 0.25 and 0.27, respectively. Poor correlations between these parameters, which have been reported previously (9, 10), appear to be due to the variability of individual data and to the relatively small treatment effects, rather than to the lack of a true relationship. The correlation coefficient between mean AUC^{24} and Au^{48} values, and between mean C_{max} and Au^{48} values for each treatment were 0.996 and 0.997, respectively.

The previous suggestion that the rate of hydrochlorothiazide excretion in urine closely resembles the time course of plasma levels (1) is confirmed in this study. Mean urinary excretion rates of hydrochlorothiazide are plotted together with plasma levels in Figs. 1–3. In each case, the overall urinary excretion rates exhibited a similar triphasic pattern to those in plasma.

The high renal clearance of hydrochlorothiazide suggests that, like chlorothiazide, it is eliminated by both renal filtration and active secretion.

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ACKNOWLEDGMENTS

Supported by Grant GM 20327, National Institutes of Health.

Pharmacokinetic Comparison of Sublingual Lorazepam with Intravenous, Intramuscular, and Oral Lorazepam

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Received May 21, 1981, from the *Division of Clinical Pharmacology, Departments of Psychiatry and Medicine, Tufts University School of Medicine* and the *New England Medical Center Hospital, Boston, MA 02111.* Accepted for publication July 7, 1981.

Abstract □ Ten healthy volunteers received single 2-mg doses of lorazepam on five occasions in random sequence. Modes of administration were: A, intravenous injection; B, deltoid intramuscular injection; C, oral tablets in the fasting state; D, sublingual dosage of oral tablets in the fasting state; and E, sublingual dosage of specially formulated tablets in the fasting state. Kinetic variables were determined from multiple plasma lorazepam concentrations meaured during 48 hr postdose. After intravenous lorazepam, mean (±*SE*) values were: elimination half-life ($t_{1/2\beta}$), 12.9 (±0.8) hr; volume of distribution, 1.3 (±0.07) liters/kg; total clearance, 1.21 (±0.1) ml/min/kg. Absorption of intramuscular lorazepam was rapid. Peak plasma levels were reached at 1.15 hr after dosage, with absorption half-life averaging 14.2 (±4.7) min. Absorption of oral and sublingual lorazepam tended to be less rapid than intramuscular injection, although differences were not significant. Times of peak concentration were 2.37, 2.35, and 2.25 hr postdose for trials C, D, and E, respectively; values of absorption half-life were 32.5, 28.5, and 28.7 min. Absolute systemic availability for trials B, C, D, and E averaged 95.9, 99.8, 94.1, and 98.2%, respectively; none of these differed significantly from 100%. Values of $t_{1/2\beta}$ were highly replicable within individuals regardless of the administration route. Thus, sublingual lorazepam is completely absorbed and is a suitable administration route in clinical practice.

Keyphrases □ Lorazepam—sublingual, pharmacokinetics compared with intravenous, intramuscular, and oral dosage forms □ Pharmacokinetics—sublingual lorazepam, comparison with intravenous, intramuscular, and oral dosage forms □ Dosage forms—sublingual lorazepam, pharmacokinetics compared with intravenous, intramuscular, and oral dosage forms

Lorazepam is a 3-hydroxy-1,4-benzodiazepine derivative in clinical use as an antianxiety and sedative agent (1, 2). Clinical situations may arise in which oral administration of a sedative is unwise or not possible, and intravenous dosage is precluded because a physician is not available. In such circumstances, intramuscular injection usually is the only alternative. The present study assessed the pharmacokinetics of lorazepam given sublingually to determine the possible clinical role of this administration route as an alternative to oral or intramuscular administration.

EXPERIMENTAL

Subjects—Ten healthy male and female volunteers, 24–39 years of age, participated after giving written informed consent (Table I). They were free of any identifiable medical disease. Subject 10 was taking oral contraceptive steroids, but no other medications were being used on a regular basis.

0022-3549/82/0200-0248$01.00/0

Table I—Subject Characteristics and Kinetics of Intravenous Lorazepam

Subjects				Lorazepam Kinetics				
Number	Age, years	Sex	Wt, kg	$t_{1/2\alpha}$, min	$t_{1/2\beta}$, hr	V_1, liters/kg	V_d, liters/kg	Clearance, ml/min/kg
1	33	F	61.4	2.8	10.9	0.39	1.24	1.32
2	24	M	70.5	3.3	7.2	0.44	1.09	1.76
3	38	M	77.3	12.0	13.1	0.30	1.08	0.96
4	29	F	61.4	1.1	15.9	0.32	1.28	0.93
5	34	M	79.5	12.6	12.2	0.53	1.59	1.51
6	25	M	63.6	13.0	14.2	0.79	1.60	1.29
7	29	M	68.1	11.2	15.2	0.58	1.19	0.91
8	32	F	50.0	10.7	14.4	1.02	1.42	1.14
9	25	F	54.5	18.6	13.9	0.50	0.99	0.82
10	26	F	57.7	1.0	12.2	0.37	1.49	1.42
			Mean (±*SE*)	8.7 (±1.9)	12.9 (±0.8)	0.52 (±0.07)	1.30 (±0.07)	1.21 (±0.10)

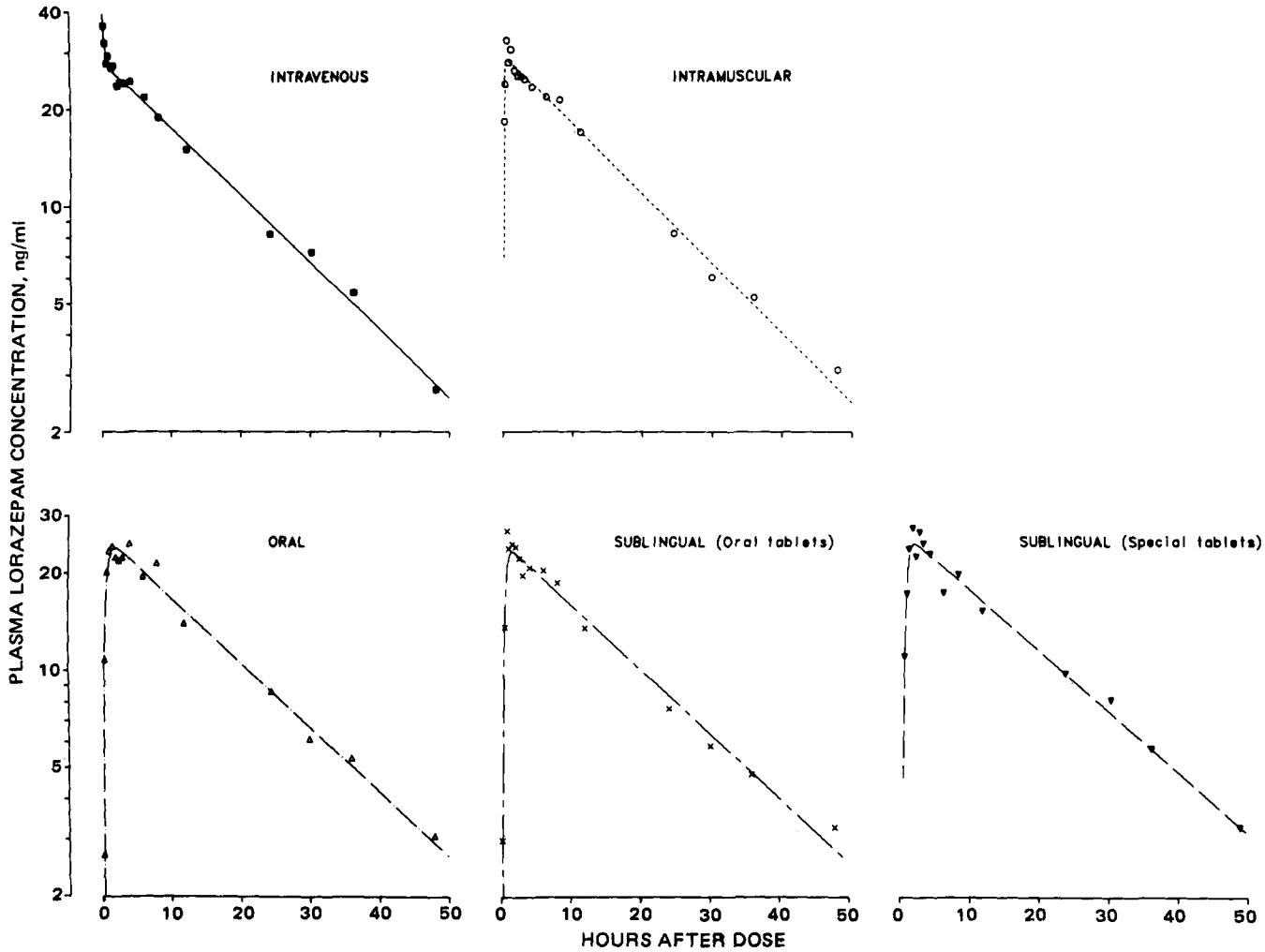

Figure 1—*Plasma lorazepam concentrations and pharmacokinetic functions of best fit following administration of lorazepam to subject 8 by each of the five administration routes.*

Design—A randomized, single-dose, five-way crossover design was utilized. Each subject received single 2-mg doses of lorazepam[1] on five occasions separated by at least 1 week. The administration modes were:

A. Intravenous lorazepam, 1 ml of a 2 mg/ml injectable preparation, infused into an antecubital vein over a 30-sec period.
B. Intramuscular lorazepam, 1 ml of the 2 mg/ml injectable preparation, given by a physician as a single deltoid intramuscular injection.
C. Oral lorazepam, administered as two standard 1-mg tablets (*in vitro* dissolution rate, 80% in 1 hr) with 100–200 ml of tap water.
D. Sublingual lorazepam, administered as two standard 1-mg oral tablets placed under the tongue and held for 15 min.
E. Sublingual lorazepam, administered as two special 1-mg sublingual tablets (*in vitro* dissolution rate, 84% in 1 hr) placed under the tongue and held for 15 min.

For trials A and B, no restrictions were placed upon the ingestion of food or liquid. For trials C, D, and E, subjects fasted overnight prior to drug administration and remained fasting for 3 hr postdose.

Procedure—Venous blood samples were drawn into heparinized tubes from an indwelling butterfly cannula or by separate venipuncture, prior to lorazepam administration, and at the following times after each dose: 5 min, and 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3, 4, 6, 8, 12, 24, 30, 36, and 48 hr. After intravenous dosage, a sample was also drawn just after the

[1] Ativan, Wyeth Laboratories, Radnor, Pa.

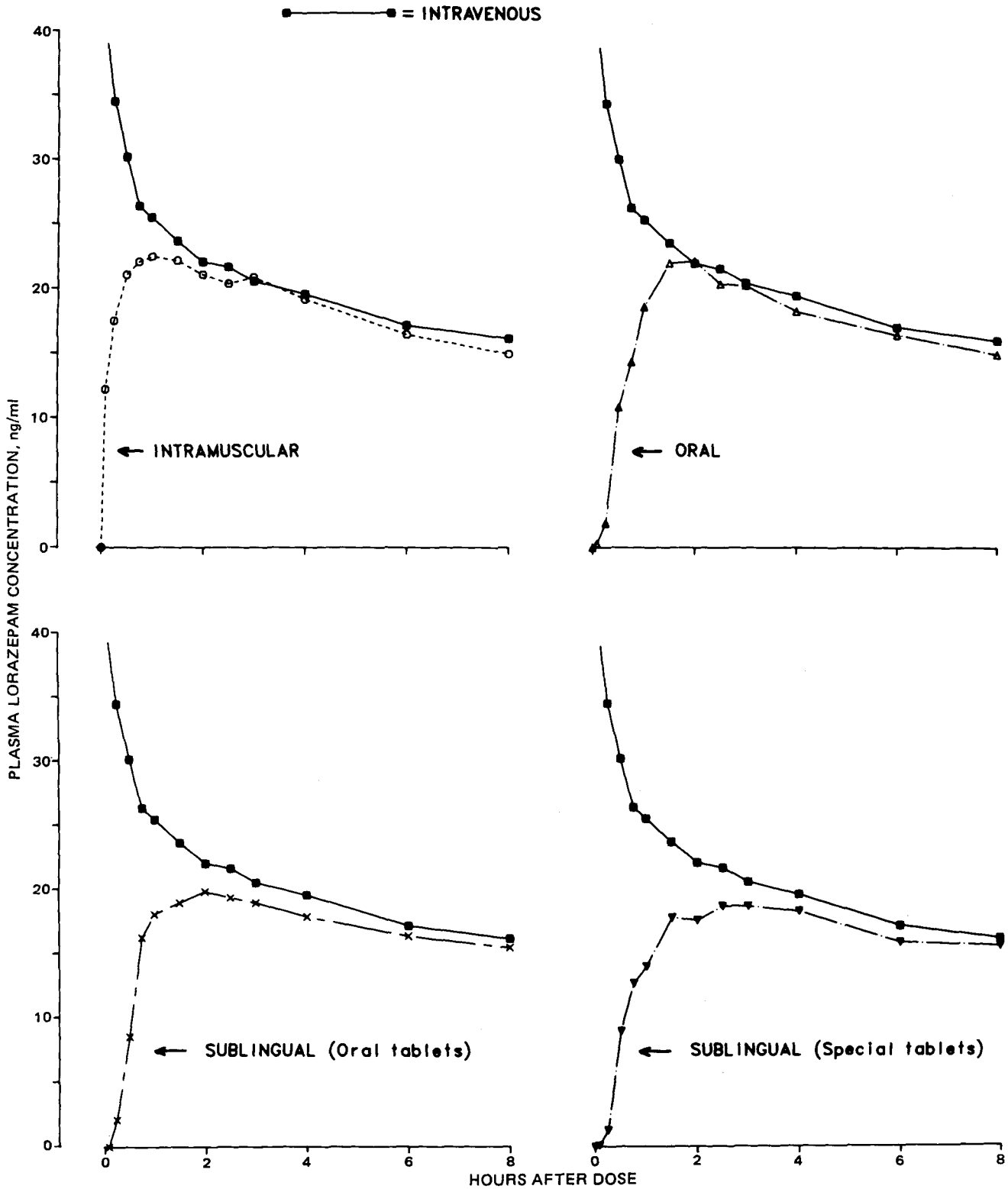

Figure 2—*Plasma lorazepam concentrations for the first 8 hr after dosage by the four extravascular administration routes compared with that observed after intravenous dosage. Each point is the mean for all 10 subjects at the corresponding time.*

infusion. Blood samples were centrifuged, and the plasma was separated and stored at −20° until assay.

Analysis of Plasma Samples—Lorazepam concentrations in all plasma samples were determined by electron-capture GLC after addition of oxazepam as the internal standard (2–4).

Analysis of Data—Plasma lorazepam concentrations following each subject trial were analyzed using iterative nonlinear least-squares regression techniques described previously (5, 6). Data points were fitted to a linear sum of exponential terms. After intravenous lorazepam, coefficients and exponents from the fitted function were used to calculate the following kinetic variables: initial (α) distribution half-life ($t_{1/2\alpha}$), elimination half-life ($t_{1/2\beta}$), volume of central compartment (V_1), total volume of distribution using the area method (V_d), total clearance, and total area under the plasma concentration curve from time zero to infinity (AUC).

After the four extravascular modes of administration, fitted functions were used to calculate the apparent half-life of absorption, lag time elapsing prior to the start of absorption (t_0), and elimination half-life ($t_{1/2\beta}$). The area under the plasma concentration curve from time zero until the last detectable plasma concentration was calculated using the

Table II—Effect of Route of Administration on Lorazepam Pharmacokinetics

Variable	Mean (±SE) Values[a] for Trial A Intravenous	B Intramuscular	C Oral	D Sublingual	E Sublingual	Value of F Two-Way ANOVA	Value of P
Peak plasma concentration, ng/ml	—	26.0 (±1.9)	24.9 (±2.4)	23.3 (±2.8)	20.7 (±1.7)	2.50	0.081
Time of peak concentration, hr postdose	—	1.15 (±0.3)	2.37 (±0.32)	2.35 (±0.7)	2.25 (±0.33)	2.32	0.098
Lag time, min	—	0	11.8 (±2.1)	22.7 (±5.1)	14.9 (±3.5)	3.29[b]	0.061
Absorption half-life, min	—	14.2 (±4.7)	32.5 (±3.8)	28.5 (±8.4)	28.7 (±7.6)	1.97	0.142
Elimination half-life, hr	12.9 (±0.8)	13.1 (±1.1)	14.1 (±1.0)	13.2 (±0.7)	14.4 (±1.0)	1.63	0.187
Systemic availability, percentage of intravenous	—	95.9 (±4.0)	99.8 (±5.7)	94.1 (±6.5)	98.2 (±5.8)	0.56	0.648

[a] Individual values are available on request. [b] Does not include value for trial B.

trapezoidal method. To this was added the residual area extrapolated to infinity, calculated at the last detectable plasma concentration divided by β, yielding the total *AUC*.

Statistical Analysis—Two-way analysis of variance was used to analyze differences in kinetic variables among the various treatments. The absolute systemic availability (completeness of absorption) of the four extravascular routes of lorazepam administration were calculated by dividing each subject's total *AUC* for a particular route of administration by the corresponding value of *AUC* following intravenous lorazepam administration to the same individual.

RESULTS

Intravenous Lorazepam (trial A)—Disappearance of lorazepam from plasma following intravenous injection was described by a linear sum of two exponential terms for subjects 1–9, and by a sum of three exponentials for subject 10. Mean kinetic variables for lorazepam were: $t_{1/2\alpha}$, 8.7 min; $t_{1/2\beta}$, 12.9 hr; V_1, 0.52 liters/kg; V_d, 1.30 liters/kg; and total clearance, 1.21 ml/min/kg (Table I).

Intramuscular Lorazepam (trial B)—All subjects noted mild to moderate local discomfort associated with the injection. This was transient and resolved shortly after the injection without specific treatment.

Peak lorazepam concentrations averaged 26 ng/ml, and were reached an average of 1.5 hr postdose (Table II, Figs. 1 and 2). In all subjects, peak plasma concentrations were reached within 3 hr of dosage. In no case did a lag time elapse prior to the start of absorption. The mean value of absorption half-life was 14.2 min (Fig. 3), and that of $t_{1/2\beta}$ was 13.1 hr. Absolute systemic availability of intramuscular lorazepam averaged 96% of the intravenous value; this was not significantly different from 100% (Table II, Fig. 4).

Oral Lorazepam (trial C)—Peak plasma lorazepam concentrations averaged 25 ng/ml and were attained an average of 2.4 hr postdose (Table II, Figs. 1 and 2). A lag time elapsed prior to the start of absorption in nine of the 10 subjects; the mean lag time was 11.8 min. The mean value of absorption half-life was 32.5 min (Fig. 3), and that of $t_{1/2\beta}$ was 14.1 hr. Mean systemic availability was 99.8% (Table II, Fig. 4).

Sublingual Lorazepam (trial D)—Peak plasma lorazepam concentrations after sublingual administration of the standard oral tablets averaged 23.3 ng/ml and were attained an average of 2.3 hr after dosage (Table II, Figs. 1 and 2). A lag time elapsed prior to the start of absorption in nine of the 10 subjects; the mean lag time was 22.7 min. The mean absorption half-life was 28.5 min, and $t_{1/2\beta}$ averaged 13.2 hr. Mean systemic availability was 94.1%.

Sublingual Lorazepam (trial E)—The kinetic profile of sublingual lorazepam administered as special tablets was very similar to that following sublingual administration of standard oral tablets described for trial D. Peak plasma concentrations averaged 20.7 ng/ml and were attained at 2.25 hr after dosage. A lag time elapsed prior to administration in eight of 10 subjects, and averaged 14.9 min. Absorption half-life averaged 28.7 min, while $t_{1/2\beta}$ averaged 14.4 hr. Mean systemic availability was 98%.

Comparison among Administration Routes—Values of $t_{1/2\beta}$ were highly consistent within subjects among the five trials (Table II, Fig. 5). Two-way analysis of variance indicated that differences attributable to administration route did not approach significance.

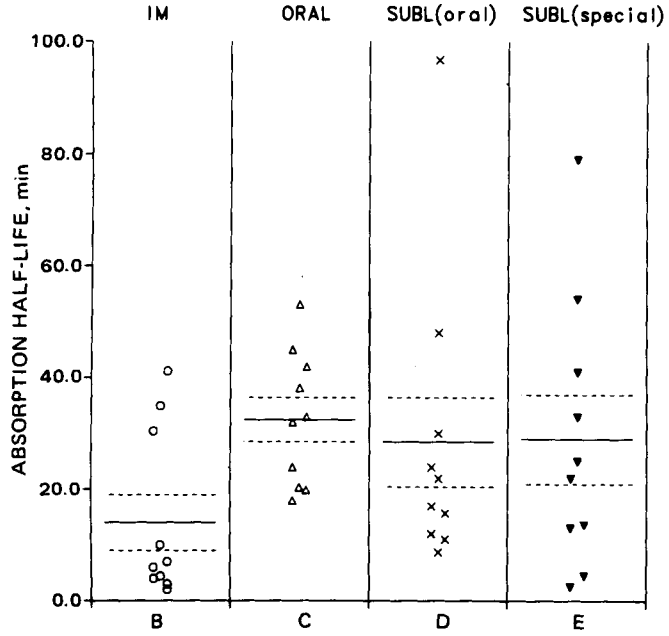

Figure 3—*Lorazepam absorption half-life following each of the four extravascular administration routes. Individual and mean (±SE) values for all subjects are shown. See Table II for statistical analysis.*

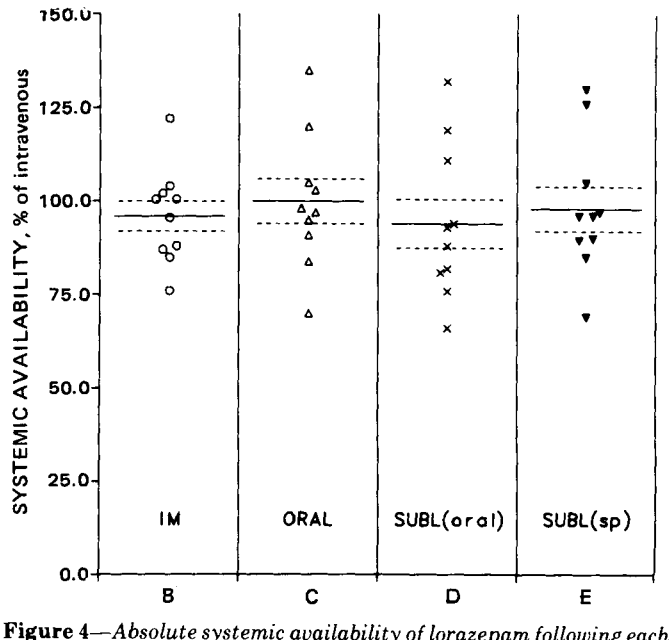

Figure 4—*Absolute systemic availability of lorazepam following each of the four extravascular administration routes. Individual and mean (±SE) values for all subjects are shown. See Table II for statistical analysis.*

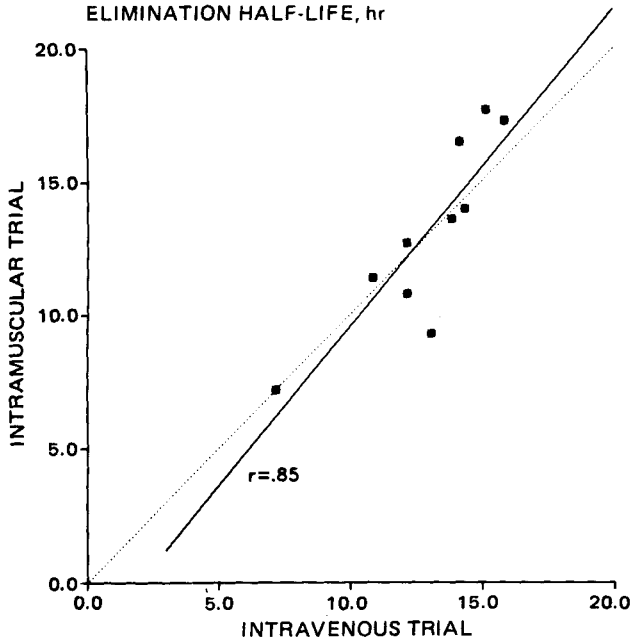

Figure 5—*Values of lorazepam elimination half-life following intravenous (trial A) and intramuscular (trial B) administration routes to the 10 subjects. Solid line was determined by least-squares regression analysis; dotted line is the line of identity.*

Differences among the four extravascular trials in peak plasma lorazepam concentrations and time of peak concentration approached but did not attain significance ($0.05 < p < 0.1$). Both variables indicated a trend for higher peak plasma levels reached sooner after the dose following intramuscular injection then after oral or sublingual administration. However, differences among trials C, D, and E were minimal (Table II). A similar trend was observed in absorption half-life. Although differences among the four extravascular trials did not reach significance, absorption half-life following intramuscular injection (trial B) was only half as long as that following the oral and sublingual routes (Table II, Fig. 3). However, differences among trials C, D, and E were minimal. Finally, no lag times were observed following intramuscular injection, whereas a lag time elapsed prior to the start of absorption in the majority of subjects following oral or sublingual administration.

Absolute systemic availability among the four extravascular modes of administration were highly comparable (Table II, Fig. 4). Mean values for trials B, C, D, and E were 96, 100, 94, and 98%, respectively. Differences among the four routes did not approach significance. Furthermore, in no case did the mean value of absolute systemic availability differ significantly from 100%.

DISCUSSION

The kinetic profile of lorazepam in the present study is similar to that reported previously from this laboratory (5–7) and elsewhere (2, 8, 9). In the present group of subjects, the range of values for $t_{1/2\beta}$ was 7–21 hr. This is similar to the range of 8–24 hr noted previously using different healthy young volunteers (5–7). It is also important to note that values of $t_{1/2\beta}$ were highly replicable within a given subject upon repeated administration of lorazepam.

The kinetics of intramuscular and oral lorazepam also are similar to patterns described previously (5–7). Deltoid intramuscular injection of lorazepam leads to rapid absorption of the drug; the completeness of absorption from the injection site is very close to 100%. Absorption of oral lorazepam is somewhat slower than that of intramuscular injection, probably due to the time required for drug dissolution and gastric emptying. Absorption of orally administered lorazepam was close to 100%.

The pattern of lorazepam absorption following sublingual administration resembles that of oral lorazepam. In the majority of cases, a lag time elapsed prior to the start of absorption, after which first-order absorption proceeded with a half-life averaging ~29 min. As in the case of oral lorazepam, the completeness of absorption of sublingual lorazepam, whether administered as standard oral tablets or specially-formulated tablets, was nearly 100%.

Thus, the rate and completeness of lorazepam absorption following sublingual administration are comparable to that observed following oral dosage on an empty stomach. In clinical terms, sublingual and oral dosage of lorazepam are likely to be therapeutically equivalent. Sublingual administration could also substitute for intramuscular injection, although the onset of clinical activity following the sublingual route may be slightly slower than that observed after intramuscular injection. Findings from the present study of sublingual lorazepam apply only to the tablet preparations studied. More rapid absorption of sublingual lorazepam might occur with formulations having more rapid dissolution rates.

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ACKNOWLEDGMENTS

Supported in part by Grant MH-34223 from the United States Public Health Service, by a Clinical Pharmacology Unit Developmental Grant from the Pharmaceutical Manufacturers' Association Foundation, and by a grant-in-aid from Wyeth Laboratories, Radnor, Pa.

The authors are grateful for the assistance of Ann Locniskar, Lawrence J. Moschitto, Ann M. Zumbo, Dr. Dean S. MacLaughlin, Dr. Darrell R. Abernethy, Dr. Hans H. Koepke, and the staff of the Clinical Study Unit, New England Medical Center Hospital (supported by USPHS Grant RR-24040).