Pharmacokinetics of Hydrochlorothiazide in Fasted and Nonfasted Subjects: A Comparison of Plasma Level and Urinary Excretion Methods

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Abstract □ The bioavailability of hydrochlorothiazide from 50-mg oral tablet doses was examined in healthy male volunteers under fasting and nonfasting conditions. Bioavailability was examined from plasma levels and urinary excretion of unchanged drug. The pharmacokinetics of hydrochlorothiazide in plasma could be described in terms of a triexponential function, and the mean drug half-lives determined from the three exponents were 1.0, 2.2, and 9.0 hr. Changing the accompanying fluid volume had no significant effect on hydrochlorothiazide absorption in fasted subjects. Plasma drug levels were significantly reduced in nonfasted individuals, compared with those in fasted individuals. A similar trend was observed in the urinary excretion of hydrochlorothiazide, but differences between treatments were not significant ($p > 0.05$). Mean 48-hr urinary recovery of hydrochlorothiazide was 70.5% of the dose in nonfasted subjects, and 73.5 and 75.0% of the dose in fasted subjects receiving the drug with 20 and 250 ml of water, respectively. The cumulative urinary excretion of hydrochlorothiazide correlated poorly ($r = 0.27$) with areas under plasma drug level curves, although the correlation between the means of these values for each of the three treatments was high ($r = 0.996$). Close similarity was observed between urinary excretion rates of hydrochlorothiazide and the time course of drug concentrations in plasma.

Keyphrases □ Hydrochlorothiazide—pharmacokinetics, fasted and nonfasted subjects □ Pharmacokinetics—hydrochlorothiazide, fasted and nonfasted subjects □ Diuretics—hydrochlorothiazide, pharmacokinetics in fasted and nonfasted subjects

High-pressure liquid chromatographic (HPLC) procedures were described to measure hydrochlorothiazide in plasma and urine (1). Preliminary clinical data obtained in that study indicated that the elimination of hydrochlorothiazide from plasma is biphasic in nature, and that its urinary excretion rate closely resembles its concentration profile in plasma.

This report describes studies in which previously described methods (1) were used to examine the plasma levels and urinary excretion of hydrochlorothiazide following single oral doses to healthy male subjects, under fasting and nonfasting conditions, and with large and small accompanying fluid volumes.

EXPERIMENTAL

Subjects—Eight male volunteers[1], 23–35 years of age (mean 28) and weighing 64–84 kg (mean 78) participated in the study after passing a physical examination and giving informed consent. No subject had a history of drug allergy.

Protocols—Subjects were instructed to take no drugs for 1 week before, and no drugs other than hydrochlorothiazide during the study. No caffeine-containing beverages were permitted from 1 day before each hydrochlorothiazide dose until the end of the plasma and urine sampling periods.

Hydrochlorothiazide[2] was administered as three single-dose oral treatments: treatment A, one 50-mg tablet with 250 ml of water, following overnight fast; treatment B, one 50-mg tablet with 20 ml of water, following overnight fast; and treatment C, one 50-mg tablet with 250 ml of water, immediately following a standard breakfast.

The treatments were administered according to a randomized crossover design, and subjects received each treatment 1 week apart.

Subjects were instructed to eat no food after 8 pm, and no liquid after 10 pm, on the day preceding each study. No further food apart from the breakfast in treatment C was permitted until 4 hr after each drug dose. After that time normal eating and drinking were permitted.

On a treatment morning, 250 ml of water was ingested on arising, at least 1 hr before dosing. The drug was administered at 8 am, the tablets being swallowed whole. No further liquid intake was permitted until 4-hr postdose. The standard breakfast consisted of cornflakes with milk, ~150 ml of orange juice, two poached eggs, two slices of toast, and a cup of caffeine-free coffee.

Blood samples (10 ml) were taken from a forearm vein into vacuum tubes[3] (containing heparin as anticoagulant) immediately before and then serially through 24-hr postdose. Urine was collected immediately before and then quantitatively at intervals through 48-hr postdose. Plasma was separated from blood by centrifugation, and plasma and urine samples were stored at −20° until assayed, generally within 2 weeks.

Analytical—Concentrations of hydrochlorothiazide in plasma and urine were determined by the HPLC methods described previously (1). The methods are linearly sensitive to hydrochlorothiazide concentrations of 2–100 μg/ml in urine, and 10–750 ng/ml in plasma. The coefficients of variation from multiple determinations within these concentration ranges were within 10% of the mean.

Analysis of the Data—Plasma hydrochlorothiazide concentrations

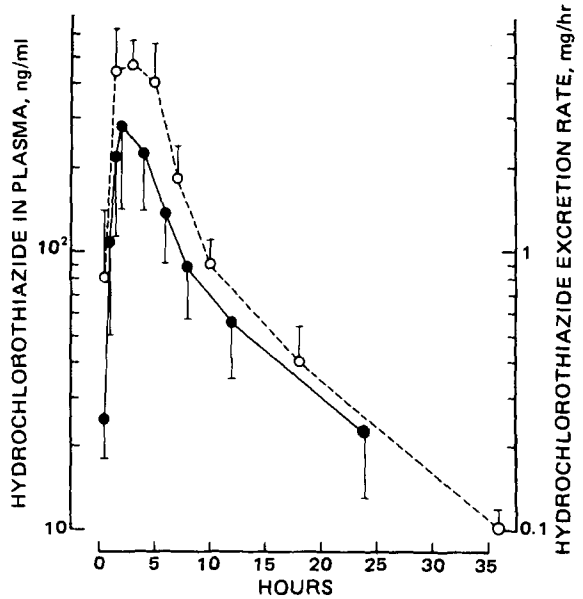

Figure 1—*Mean plasma concentrations (●) and urinary excretion rates, (○) of hydrochlorothiazides following treatment A, 50-mg tablet dose with 250 ml of water on a fasted stomach. Error bars indicate ±1* SD.

[1] Technical staff and graduate students.

[2] Hydrodiuril 50-mg tablets, lot B0686, Merçk Sharp and Dohme, West Point, Pa.

[3] Vacutainer.

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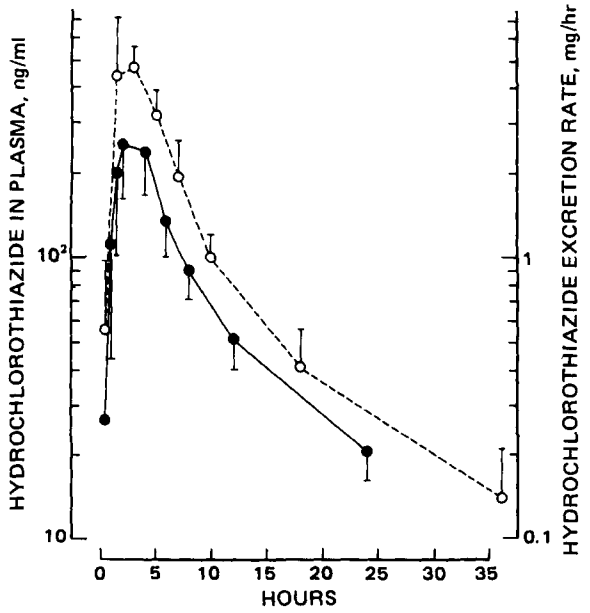

Figure 2—*Mean plasma concentrations (●) and urinary excretion rates (○) of hydrochlorothiazide following treatment B, 50-mg tablet dose with 20 ml of water on a fasted stomach.*

from each individual subject were fitted to a triexponential function of the form:

$$C = Xe^{-\alpha t} + Ye^{-\beta t} + Ze^{-\gamma t} \qquad \text{(Eq. 1)}$$

where C is the drug concentration in plasma at time t and other values are constants.

Initial estimates of parameter values were obtained by standard graphical methods. Improved estimates, together with statistical analysis, were obtained by nonlinear regression using the NREG computer program (2). Plasma hydrochlorothiazide levels at each sampling time, urinary excretion data, and pharmacokinetic parameter values were examined for subject and treatment effects by analysis of variance for crossover design. When significant treatment effects were obtained by analysis of variance, differences between treatments were examined by Tukey's test (3).

Reagents—The sources of reagents and solvents were described previously (1).

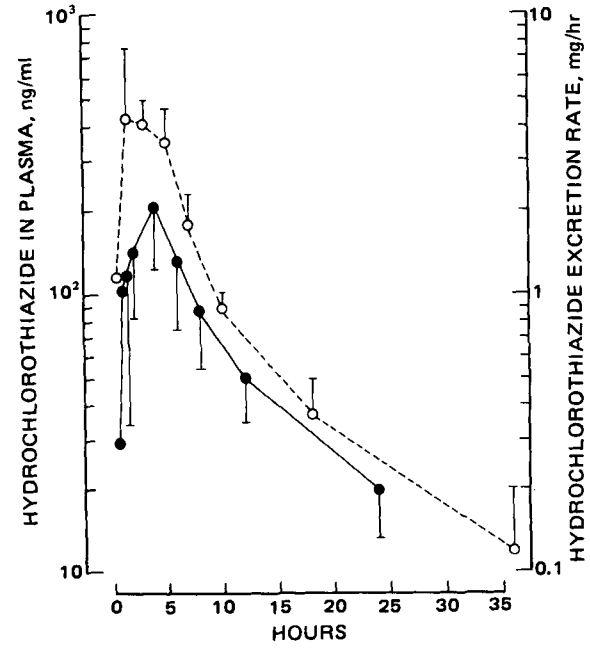

Figure 3—*Mean plasma concentrations (●) and urinary excretion rates (○) of hydrochlorothiazide following treatment C, 50-mg tablet dose with 250 ml of water immediately following a standard meal.*

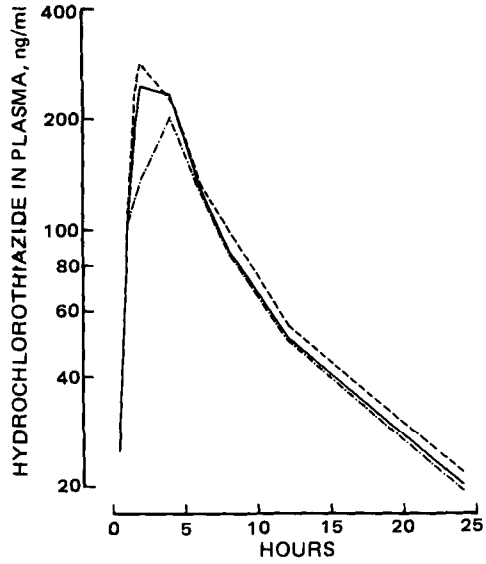

Figure 4—*Mean plasma concentrations of hydrochlorothiazide following treatments A (– –), B (—), and C (– · – ·).*

RESULTS

Plasma Hydrochlorthiazide Levels—The mean plasma hydrochlorothiazide concentration curves from the three treatments are shown in Figs. 1–3. For comparison between treatments, the curves are combined in Fig. 4.

The mean plasma drug profiles obtained from the two fasting treatments were almost identical. Mean peak drug concentrations of 310 and 291 ng/ml were obtained ~2.5-hr postdosing from treatments A and B, respectively (Table I). After this time, the drug levels declined rapidly to 12 hr, and at a slower rate to 24 hr.

The nonfasting dose of hydrochlorothiazide yielded drug profiles in plasma similar to the fasting treatments, but the drug concentrations tended to be lower. Plasma drug levels from treatment C were significantly lower ($p < 0.05$) than those from treatment A at 2 hr, and from treatment B at 4 hr. From Table I, the C_{max} and AUC^{24} values from treatment C were significantly lower than those from treatment A, while treatment B yielded intermediate values.

Analysis of individual drug curves in terms of Eq. 1 yielded the numerical values for the rate constants α, β, and γ shown in Table II. Almost identical mean values were obtained for each of the constants from the different treatments. The mean coefficients of determination, r^2, obtained from nonlinear regression analysis $[(\Sigma obs^2 - \Sigma dev^2)/\Sigma obs^2]$ were 0.91 ± 0.03, 0.93 ± 0.06, and 0.92 ± 0.08 for treatments A, B, and C, respectively.

Urinary Excretion of Hydrochlorothiazide—The mean cumulative urinary recovery of hydrochlorothiazide at each collection interval is shown in Fig. 5. The 24- and 48-hr mean recovery values are given in Table I. Overall recovery of hydrochlorothiazide was 75.0, 73.5, and 70.5% of the dose from treatments A, B, and C, respectively. While urinary recovery exhibited a similar trend to plasma levels, there were no significant

Table I—Pharmacokinetic Parameter Values (±1 *SD*, *n* = 8) for Hydrochlorothiazide

Parameter	Value: Treatment A	Value: Treatment B	Value: Treatment C	Statistical Significance
C_{max}[a], ng/ml	310 ± 130	291 ± 80	241 ± 66	$\overline{A\ B\ C}$
T_{max}[b], hr	2.4 ± 1.8	2.6 ± 1.2	2.9 ± 1.5	NSD[c]
AUC^{24}[d], ng hr/ml	2097 ± 717	2018 ± 450	1777 ± 384	$\overline{A\ B\ C}$
AU^{24}[e], %	69.0 ± 8.5	66.7 ± 8.6	64.3 ± 6.1	NSD
Au^{48}[f], %	75.0 ± 8.4	73.5 ± 10.1	70.5 ± 9.3	NSD
R_{cl}[g], ml/min	307 ± 124	292 ± 93	320 ± 100	NSD

[a] Maximum concentration of hydrochlorothiazide in plasma. [b] Time of C_{max}. [c] No significant differences. [d] Area under hydrochlorothiazide concentration curve in plasma from zero to 24 hr, calculated by trapezoidal rule. [e] Cumulative 24-hr urinary excretion of hydrochlorothiazide. [f] Cumulative 48-hr urinary excretion of hydrochlorothiazide. [g] Renal clearance of hydrochlorothiazide, calculated by dividing Au^{24} by AUC^{24}.

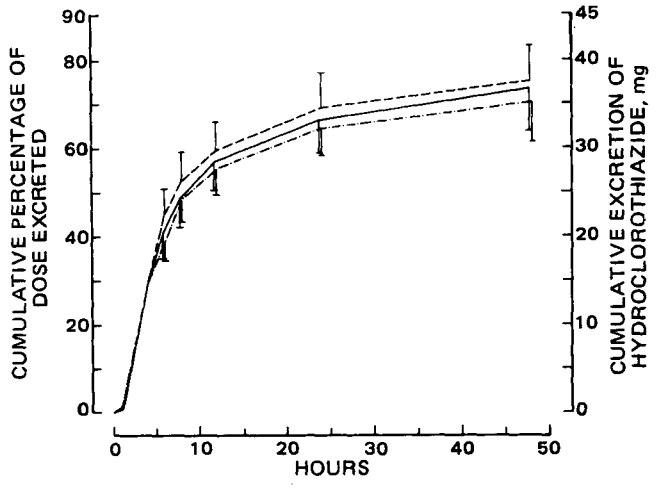

Figure 5—*Mean cumulative excretion of hydrochlorothiazide in urine following treatments A (– –), B (—), and C (– · – ·).*

differences in the urinary recovery from the different treatments. The renal clearance of hydrochlorothiazide was ~300 ml/min, and there were no significant treatment effects in this value.

DISCUSSION

Information on the pharmacokinetics and bioavailability of the thiazide diuretics has been restricted by a lack of suitable analytical procedures. Early studies utilized colorimetry (4) but HPLC methods are now favored because of their greater sensitivity and specificity (5). Plasma hydrochlorothiazide concentrations are approximately 100-fold lower than those in urine, and previous studies concerning plasma drug levels have used gas chromatography with electron-capture detection (6–8).

The HPLC procedures used in this study are suitable for analysis of both urine and plasma hydrochlorothiazide levels following single therapeutic doses. Initial studies using these assay procedures (1) indicated that elimination of hydrochlorothiazide from plasma was biphasic. They also suggested that, while there is poor agreement between the areas under plasma level curves and cumulative urinary excretion of hydrochlorothiazide (9, 10), there is close similarity between the time course of plasma drug levels and urinary excretion rates.

The present study confirms these observations. While the biphasic decline of drug levels in plasma is based largely on data points obtained at 12 and 24 hr, this elimination pattern was reported previously (1, 9). The half-lives calculated from the mean values of γ, α, and β in Table II are ~1.0, 2.2, and 9.0 hr, respectively, and these values were unaffected by the different treatments. The largest of these, the terminal half-life for hydrochlorothiazide in plasma, is similar to values reported previously (1, 10).

The mechanism underlying biphasic elimination of hydrochlorothiazide from plasma is unclear. Hydrochlorothiazide accumulates in erythrocytes, but equilibrium of drug between plasma water and blood cells is reached in 4 hr after an oral dose (10). The pattern of hydrochlorothiazide elimination from plasma is different from that of chlorothiazide. In the case of hydrochlorothiazide, biphasic elimination is clearly evident in individual subjects, as shown in Fig. 6. However, in the case of chlorothiazide, while mean plasma levels could be described by a triexponential function, profiles in individual subjects were erratic and exhibited a sawtooth effect (11, 12).

The plasma drug levels obtained from the different treatments showed that the efficiency of hydrochlorothiazide absorption from oral tablets was not markedly influenced by fluid volume, but decreased when the drug was taken after a meal. The urinary excretion data showed a similar trend, but the treatment effects on drug excretion were not significant.

Table II—Values of Rate Constants (±1 *SD*, $n = 8$) Obtained by Fitting Individual Plasma Hydrochlorothiazide Profiles to Eq. 1

Treatment	Rate Constant, hr^{-1}		
	α	β	γ
A	0.32 ± 0.08	0.078 ± 0.18	0.67 ± 0.22
B	0.32 ± 0.08	0.078 ± 0.18	0.65 ± 0.52
C	0.28 ± 0.09	0.078 ± 0.011	0.74 ± 0.52

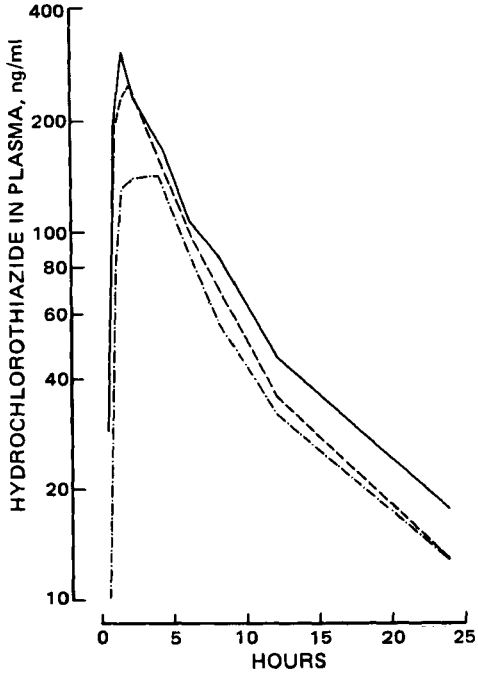

Figure 6—*Plasma concentrations of hydrochlorothiazide in one subject following treatments A (– –), B (—), and C (– · – ·).*

These results are inconsistent with a previous report in which hydrochlorothiazide absorption was increased by food (7). Procedural differences between the studies may account for this. In the present study, both fasted and nonfasted subjects were permitted normal food intake after 4-hr postdosing. In the previous study, fasted subjects received no solid food until 10-hr postdosing, while nonfasted subjects received three regular meals during that period. Prolonged abstinence from food by the fasted subjects may have affected drug absorption due to altered GI secretion and motility. The previous study also employed a higher dose of hydrochlorothiazide (75 mg).

The different effects of food on the GI absorption of hydrochlorothiazide and chlorothiazide (11) are possibly related to dose size. Chlorothiazide was shown to be poorly absorbed from 250 and 500 mg doses; less than 25% of the administered dose was recovered in urine (12, 13). Absorption was improved to only a small extent when chlorothiazide was administered as a solution, compared to tablets (12, 13), but doubled when chlorothiazide tablets were administered immediately following a meal (11). However, hydrochlorothiazide was efficiently absorbed from 50–75-mg oral doses (6–9).

The poor bioavailability of oral chlorothiazide may be due to saturable and site-specific absorption (5, 11). The structural similarity of the two compounds suggests that hydrochlorothiazide may be absorbed by a mechanism similar to chlorothiazide, but the lower dose of hydrochlorothiazide precludes saturation of the absorption mechanism. While food may increase the bioavailability of oral chlorothiazide by reducing the rate at which drug is presented to the absorption site (11), this mechanism would be less important for lower doses of hydrochlorothiazide. The inhibitory effects of food appear to dominate with this compound (14, 15), but these effects are small and are unlikely to be clinically significant.

The negligible effect of altered fluid volume on hydrochlorothiazide absorption was unexpected. Hydrochlorothiazide has a low aqueous solubility (9), and large accompanying fluid volumes have been shown to increase the absorption of a number of lipophilic drugs (16). Previously, increased absorption has been attributed to more efficient drug dissolution or faster stomach emptying (14). In the case of hydrochlorothiazide, these effects appear to be negligible. This is possibly related to the efficient absorption of hydrochlorothiazide in general; an increase in absorption due to increased fluid volume would be difficult to detect. It could be speculated that any potential increase in drug release in the GI tract may be offset by saturable absorption, but other studies would be needed to confirm this.

Although an official dissolution test exists for hydrochlorothiazide tablets (17), there have been differing reports on the ability of *in vitro* dissolution rates to accurately predict *in vivo* drug bioavailability (18, 19).

Correlations between individual areas under hydrochlorothiazide

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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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.

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