as that of ethionamide. When the potential was plotted against the logarithm of the drug concentration, a linear calibration plot was obtained in the drug concentration range of 2×10^{-5}–1×10^{-2} M.

The amount of drug was first determined with the pure drug powder. According to USP XX (5), ethionamide contains ≥98.0% and ≤102.0% of $C_8H_{10}N_2S$, calculated on an anhydrous basis. Prothionamide is described only in the JP X (6), and not in the USP or British Pharmacopeia (7). According to the Japanese Pharmacopeia, prothionamide determined on a dry weight basis should be >98.0% pure.

The recovery of the drugs is shown in Table II. Determinations were performed on eight samples of both drugs. The amounts of ethionamide and prothionamide were estimated with the same average errors of 0.03%, and the standard deviations were 0.15 and 0.20, respectively. The recoveries were good and reproducible.

Determinations on both tablets were carried out. A suitable extraction solution was sought. Both drugs are very soluble in methanol and glacial acetic acid and are also soluble in ethanol and acetone; however, in the extraction it is necessary to avoid interference from extraneous compounds. Methanol is used in the USP procedure. The tablets were therefore extracted with methanol and after evaporation of the methanol, the residue was heated at reflux with 20% HCl. After heating for 3 hr, the solution became brown, and a brown precipitate separated out. Evidently the precipitate resulted from impurities dissolved in the methanol.

The tablets were then extracted with acetone. After dissolution in acetone, the solution was centrifuged. This was found to be the best method because filtration of the acetone solution proved to be difficult. The extraction was carried out four or five times until the extract was colorless. The solvent was evaporated, and the residue was heated at reflux for 1 hr with 20% HCl to give a light-brown precipitate and a pale-brown solution. The acidic solution was then neutralized with sodium hydroxide at pH 6.5, and the resulting mixture was subjected to potentiometric measurements. Determinations were performed on five samples of 20 tablets. According to the USP XX, ethionamide tablets contain ≥95.0% and ≤110% of the labeled amount of drug. The results obtained are shown in Table III. The mean recoveries for ethionamide and prothionamide tablets were 100.46 and 100.42%, respectively, and the respective standard deviations were 0.36 and 0.28. The labeled amount of drugs was 100 mg/tablet. The recoveries are given compared with the theoretical amount of ammonia in the drug tablets, and it is believed that one tablet indeed contains 100 mg.

CONCLUSION

The assay method for the drugs in JP X is based on the nonaqueous titration method using perchloric acid; however, the color change is not sharp. In the BP, the end-point is determined potentiometrically, which alleviates this problem. In USP XX, a colorimetric method is used for the determination of the pure powder and tablets. The procedure is accurate, but nonspecific.

The proposed method for the assay of drugs having a carbothionamido group is simple and specific. The recovery is satisfactory and lies within acceptable limits. In view of this, use of the ammonia gas-sensing electrode is recommended as a possible pharmacopeial method.

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Pharmacokinetics of Chlorzoxazone in Humans

RAVI K. DESIRAJU ˣ, NED L. RENZI, Jr., RAMCHANDRA K. NAYAK, and KUNG-TAT NG

Received March 5, 1982, from the *Department of Drug Metabolism, McNeil Pharmaceutical, Spring House, PA 19477.* Accepted for publication August 6, 1982.

Abstract □ Twenty-three normal male subjects received 900 mg of acetaminophen and 750 mg of chlorzoxazone as an oral suspension. Analysis of plasma samples indicated a rapid absorption and rapid elimination of chlorzoxazone. Average values of the elimination half-life and plasma clearance were 1.12 ± 0.48 hr and 148.0 ± 39.9 ml/min, respectively. Analysis of urine samples showed that chlorzoxazone was eliminated from the body as the glucuronide conjugate of the intermediate metabolite 6-hydroxychlorzoxazone, to the extent of 74% of the dose. The plasma and the urinary excretion data were fitted to theoretical equations, and excellent fits were obtained using a five-parameter pharmacokinetic model.

Keyphrases □ Chlorzoxazone—analysis in human plasma and urine, administration with acetaminophen; pharmacokinetics □ Pharmacokinetics—chlorzoxazone, analysis in human plasma and urine, concomitant administration with acetaminophen □ Acetaminophen—concomitant administration with chlorzoxazone, analysis in human plasma and urine, effect on pharmacokinetics

Chlorzoxazone (5-chloro-2(3*H*)-benzoxazolone) (I) is a potent skeletal muscle relaxant that is effective in the treatment of skeletal muscle spasms. Onset of therapeutic activity is observed within 1 hr, with a duration usually up to 6 hr (1). Chlorzoxazone exhibits minimal adverse effects and almost no GI irritation.

The data and results presented in this report are part of a study that was performed with 23 normal male subjects to determine the bioavailability of acetaminophen and chlorzoxazone from a commercial combination tablet formulation and an oral suspension. While there exists sufficient information in the literature regarding acetaminophen elimination kinetics (2–6), little has been reported on the disposition characteristics of chlorzoxazone in humans. This report deals primarily with the plasma levels and urinary excretion of chlorzoxazone following administration of a suspension of chlorzoxazone and acetaminophen.

In studies dealing with the metabolic fate of chlorzoxazone in humans, Conney and Burns (7) reported that <1% of the drug was excreted unchanged in urine. Chlorzoxazone was rapidly metabolized in humans to 6-hydroxy-

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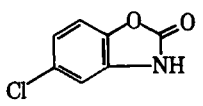

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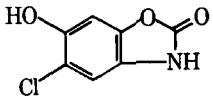


II

chlorzoxazone (5-chloro-6-hydroxy-2(3*H*)-benzoxazolone) (II) which was excreted in urine primarily as the glucuronide conjugate. They could not detect any 6-hydroxychlorzoxazone in the urine in the free form. Their *in vitro* experiments utilizing liver homogenates of rat, rabbit, mouse, and guinea pig established the liver as the principal site of metabolism and 6-hydroxychlorzoxazone as the major metabolite of the *in vitro* metabolism of chlorzoxazone. In this investigation, we have attempted to obtain the pharmacokinetic parameters of chlorzoxazone in humans when administered concomitantly with acetaminophen.

EXPERIMENTAL

Subject Selection—Twenty-three normal, healthy, adult male subjects (20–39 years of age) participated in this study. They were found to be in good health as determined by a screening procedure consisting of a physical examination, evaluation of clinical laboratory values (hematology, blood chemistry, and urinalysis), and determination of vital signs. None of the subjects had any serious diseases, and they refrained from taking drugs for a period of 2 weeks prior to this study.

Dose Administration—The subjects, after fasting for a minimum period of 12 hr, received 900 mg of acetaminophen and 750 mg of chlorzoxazone as an oral suspension. Each milliliter of the aqueous suspension contained 15 mg of chlorzoxazone, 18 mg of acetaminophen, and 5 mg of tragacanth (as a 0.5% solution).

Blood samples (10 ml) were drawn from the subjects at 0 (predose), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, and 10 hr after dosing. The samples were collected in heparinized tubes[1], stored in ice, and centrifuged as soon as possible to obtain plasma.

Urine samples were obtained from pooled samples collected for the following time periods: 0 (predose), 0–2, 2–4, 4–6, 6–8, and 8–10 hr after dosing. The pH and total volume of the pooled sample for each time period were recorded. A 50-ml aliquot of each pooled sample was transferred to a container and frozen.

Analytical Procedures—*Analysis of Plasma Samples for Acetaminophen*—To a 2-ml plasma sample in a 35-ml screw-cap centrifuge tube were added 1 ml of phosphate buffer (pH 7.4), 1.0 ml of ethyl acetate solution containing 20 μg/ml of *N*-butyl-*p*-aminophenol (internal standard), 1.0 g of solid sodium chloride, and 9.0 ml of ethyl acetate. The tube was shaken for 10 min and centrifuged at 2000 rpm for 10 min. Nine milliliters of ethyl acetate was transferred to another 35-ml centrifuge tube containing 2.0 ml of 5% sodium phosphate (pH 11.9). After centrifugation, the ethyl acetate was aspirated off. To the aqueous layer, 1.0 ml of sodium phosphate monobasic buffer (pH 4.5) and 11.0 ml of ethyl acetate were added. The tube was shaken for 10 min and centrifuged for 10 min. Ten milliliters of the ethyl acetate (upper) layer was transferred to a 15-ml conical screw-cap centrifuge tube and evaporated to dryness under a nitrogen stream. The residue was dissolved in 5 μl of pyridine and 15 μl of acetic anhydride, and the tube was placed in a thermostated water bath at 42° for 20 min.

Two microliters of the resulting acetylated reaction mixture was injected into a gas chromatograph[2] using the following conditions: the glass column (91.5 cm × 2-mm i.d.) was packed with 3% OV-17 on 80/100 mesh Chromosorb G-HP. The injection port, column, and detector (FID) temperatures were 220°, 165°, and 220°, respectively. The carrier gas (nitrogen) flow rate was 25 ml/min; hydrogen and air flow rates were 25 and 300 ml/min, respectively. The retention times of acetaminophen and the internal standard were 8.5 and 15.0 min, respectively. The calibration curve was linear from 0.5 to 20.0 μg/ml.

Analysis of Plasma Samples for Chlorzoxazone—Sample preparation involved a single-step extraction and derivatization. One milliliter of plasma was pipetted into a 15-ml disposable bottle containing 1 ml of 0.5 *N* HCl. To this was added 10 ml of ethyl acetate containing 20 μg of the internal standard (*n*-hexadecane). The mixture was shaken for 10 min and centrifuged at 2000 rpm for 5 min. A 9-ml aliquot of the ethyl acetate layer was transferred to a 15-ml screw-cap centrifuge tube and evaporated to ~0.5 ml under a nitrogen stream. The sides of the tubes were rinsed with an additional 0.5 ml of ethyl acetate. The combined ethyl acetate solution was evaporated to dryness. To the residue were added 5 μl of pyridine and 15 μl of acetic anhydride. The tube was capped and placed in a water bath at 42° for 20 min.

A 2-μl aliquot of the resulting reaction mixture was injected into a gas chromatograph equipped with a dual flame-ionization detector. The columns were 1.83 m × 4-mm i.d. glass tubes packed with 3% OV-1 on 60/80 mesh Gas Chrom Q. Column temperature was maintained at 130°. The carrier gas (nitrogen) was held at a flow rate of 30 ml/min; the hydrogen and air flow rates were 30 and 300 ml/min, respectively. The retention times of chlorzoxazone and the internal standard were 3.25 and 4.5 min, respectively. The lower limit of quantitation was 0.5 μg/ml using 1 ml of plasma. The calibration curve was found to be linear between 0.5 and 25 μg/ml. Extraction efficiency for chlorzoxazone under the above conditions was 88 ± 8% (six determinations).

Table I—Mean Peak Plasma Concentrations, Peak Times, and AUC (0–10 hr) of Acetaminophen and Chlorzoxazone in 23 Normal Subjects Following Oral Administration of Acetaminophen and Chlorzoxazone [a]

Drug	Parameter, mean ± *SEM*		
	Peak Plasma Concentration, μg/ml	Peak Time, min	AUC (0–10 hr) μg·min/ml
Acetaminophen	16.7 ± 1.3	40 ± 9.4	2816 ± 170
Chlorzoxazone	36.3 ± 2.3	38 ± 3.3	4084 ± 284

[a] Administered as a suspension containing 900 mg of acetaminophen and 750 mg of chlorzoxazone.

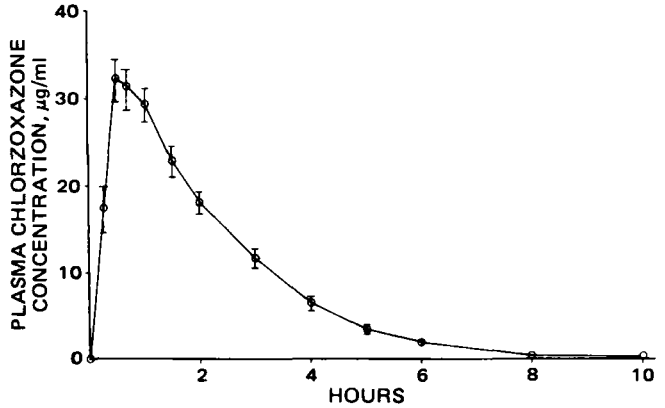


Figure 1—*Mean (±SEM) plasma concentrations of chlorzoxazone (μg/ml) in 23 human subjects following the oral administration of 900 mg of acetaminophen and 750 mg of chlorzoxazone.*

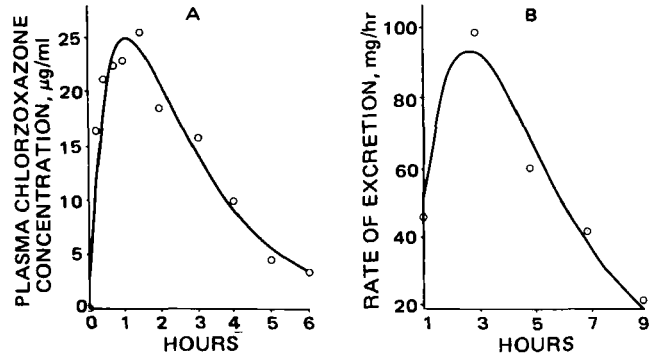


Figure 2—*Computer-fitted profiles (—) of plasma chlorzoxazone data (A) and urinary excretion data (B) of 6-hydroxychlorzoxazone glucuronide as chlorzoxazone equivalents obtained for a subject. Circles represent observed data.*

[1] Vacutainer, Becton, Dickinson and Co.

[2] Varian Aerograph (Model 2400).

Table II—Pharmacokinetic Parameters of Chlorzoxazone in Humans [a]

	V/f, liters	K, hr^{-1}	k_a, hr^{-1}	k_{m1}, hr^{-1}	k_{u2} hr^{-1}	$t_{1/2}$, hr	KV/f, ml/min [b]
Average of individual values [c]	13.70 ± 5.07	0.73 ± 0.29	2.28 ± 2.08	0.63 ± 0.31	0.60 ± 0.31	1.12 ± 0.48	148.0 ± 39.9
Evaluation of mean data [d]	13.89 ± 1.85	0.69 ± 0.13	1.96 ± 0.35	0.53 ± 0.10	0.42 ± 0.04	1.00	159.7

[a] Expressed as mean ± *SD*. [b] Clearance/*f*. [c] $n = 22$; one subject was excluded due to nonconvergence of k_a. [d] $n = 23$.

Analysis of Urine Samples for 6-Hydroxychlorzoxazone and Acetaminophen—The assay was designed to quantitate simultaneously total acetaminophen (intact plus glucuronide and sulfate conjugates) and total 6-hydroxychlorzoxazone (intact and glucuronide conjugate) in urine. Intact chlorzoxazone has been reported to be present in urine at ≤1% of the dose (7).

Aliquots (0.5 ml) of urine samples containing acetaminophen, 6-hydroxychlorzoxazone, their conjugates, and the added internal standard (*N*-butyl-*p*-aminophenol, 200 μg) were incubated overnight with β-glucuronidase[3] in an acetate buffer (pH 4.6) at 37°. The enzymatically hydrolyzed products were then extracted by adjusting the urine sample pH to 7.4 with 1 ml of phosphate buffer (pH 11.9) and extracting with 5 ml of ethyl acetate. A 4-ml aliquot of the ethyl acetate was then extracted with 3 ml of phosphate buffer (pH 11.9). The ethyl acetate was aspirated off and 1 ml of phosphate buffer (pH 4.5) was added to neutralize the solution. The neutralized solution was again extracted with 5 ml of ethyl acetate. Four milliliters of the ethyl acetate layer was evaporated to dryness under a nitrogen stream, and the residue was reconstituted with 50 μl of methanol.

Ten microliters of the methanolic solution was injected into a liquid chromatograph[4] equipped with a UV detector[5] at a wavelength of 280 nm. The reverse-phase analytical column[6] was 25 cm in length and 4.6-mm i.d. The mobile phase was water–methanol–pH 4.6 acetate buffer (3:1:1, v/v/v). The flow rate was held at 2 ml/min. The retention times for acetaminophen, 6-hydroxychlorzoxazone, and the internal standard were 3, 9, and 11 min, respectively. The calibration curve was linear from 20 to 1000 μg/ml for both acetaminophen and 6-hydroxychlorzoxazone. The extraction efficiencies for 6-hydroxychlorzoxazone and acetaminophen under the above conditions were 86 ± 6.5 and 95 ± 10.7%, respectively (six determinations).

RESULTS AND DISCUSSION

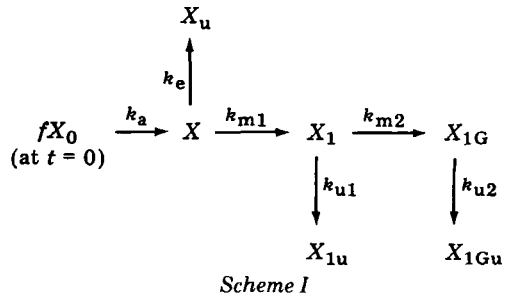
Table I lists a summary of acetaminophen peak plasma concentrations, peak times, and the area under the plasma concentration–time curve (AUC 0–10 hr) as calculated by the trapezoidal rule, observed in 23 normal subjects following the oral administration of 900 mg of acetaminophen and 750 mg of chlorzoxazone. Acetaminophen was rapidly absorbed with a mean peak plasma concentration of 16.7 μg/ml at a mean peak time of 40 min. These values are in the range of values obtained by other investigators (5), thus showing that the disposition kinetics of acetaminophen were not altered by the concurrent administration of chlorzoxazone.

Table I also lists the pharmacokinetic parameter values for chlorzoxazone. The mean (± *SEM*) plasma chlorzoxazone concentration–time profile is shown in Fig. 1. Chlorzoxazone was rapidly absorbed, attaining a mean (±*SEM*) peak level of 36.3 ± 2.3 μg/ml at a mean peak time of 38 ± 3.3 min after dosing. After reaching a peak, the plasma concentrations declined rapidly in a monoexponential manner, suggesting a rapid distribution. Plasma concentrations at the 8- and 10-hr time points for most subjects were either zero or were below the assay quantitation limit of 0.5 μg/ml, indicating that chlorzoxazone was rapidly eliminated from the body. The individual and mean plasma chlorzoxazone concentration–time profiles following the oral administration of chlorzoxazone were found to be characteristic of a one-compartment oral absorption model conforming to:

$$C_t = \frac{k_a f X_0}{V(k_a - K)}\left[e^{-Kt} - e^{-k_a t}\right] \qquad \text{(Eq. 1)}$$

where C_t is the concentration of chlorzoxazone in plasma at time t, k_a is the apparent first-order absorption rate constant, X_0 is the dose of chlorzoxazone (750 mg), f is the fraction of the administered dose reaching systemic circulation as unchanged chlorzoxazone, K is the apparent first-order elimination rate constant of the drug, and V is the apparent volume of distribution.

The urinary excretion data revealed that at the end of 10 hr, 74 ± 3.4% (mean ± *SEM*) of the dose was excreted as 6-hydroxychlorzoxazone glucuronide. Based on the information available in the literature (7), the biotransformation profile of chlorzoxazone could be explained by:

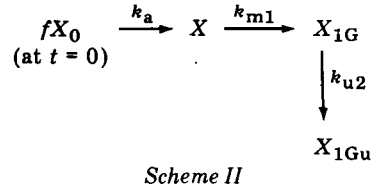


Scheme I

where X and X_u are the amounts of chlorzoxazone in the body and urine, respectively; X_1 and X_{1u} are the amounts of 6-hydroxychlorzoxazone in the body and urine, respectively; X_{1G} and X_{1Gu} are the amounts of 6-hydroxychlorzoxazone glucuronide in the body and urine, respectively; k_e, k_{u1}, and k_{u2} are the renal excretion rate constants for chlorzoxazone, 6-hydroxychlorzoxazone, and 6-hydroxychlorzoxazone glucuronide, respectively; and k_{m1} and k_{m2} are the respective metabolic rate constants for the formation in the body of 6-hydroxychlorzoxazone from chlorzoxazone and 6-hydroxychlorzoxazone glucuronide from 6-hydroxychlorzoxazone.

Under the conditions of the analytical procedure employed in this study, neither unchanged chlorzoxazone nor 6-hydroxychlorzoxazone could be detected in the urine samples. Although the lower limit of quantitation was established at 20 μg/ml, the assay was capable of detecting 5 μg/ml of 6-hydroxychlorzoxazone in urine. When the urine samples were hydrolyzed by β-glucuronidase and then assayed, 6-hydroxychlorzoxazone was detected indicating the presence of 6-hydroxychlorzoxazone glucuronide in the urine samples prior to hydrolysis.

Since 6-hydroxychlorzoxazone was not detected in the urine samples (or was present in negligible amounts), the biotransformation pathway in Scheme I was simplified to give:



Scheme II

In proposing this simplified model, the following assumptions were made:

1. The absence of 6-hydroxychlorzoxazone in the urine samples is due to its rapid conversion in the body to the glucuronide conjugate, *i.e.*, $k_{m1} <<< k_{m2}$ or k_{m1} is the limiting rate constant.
2. The absence of 6-hydroxychlorzoxazone in urine is not due to its reabsorption from the kidney since 6-hydroxychlorzoxazone is sufficiently polar in nature to be excreted by the kidney, *i.e.*, $k_{u1} \simeq 0 <<< k_{m2}$. For this model, the amount of 6-hydroxychlorzoxazone glucuronide excreted in urine as a function of time is given as (8):

$$\frac{d(X_{1Gu})}{dt} = k_{u2}k_{m1}k_a f X_0 \left[\frac{e^{-k_a t}}{(K - k_a)(k_{u2} - k_a)} + \frac{e^{-Kt}}{(k_a - K)(k_{u2} - K)} + \frac{e^{-k_{u2}t}}{(k_a - k_{u2})(K - k_{u2})}\right] \qquad \text{(Eq. 2)}$$

[3] Glusulase, Endo Laboratories, Garden City, N.J.
[4] Waters Associates, Milford, Mass.
[5] Model 440.
[6] Hibar-II, LiChrosorb, RP-18; E. Merck.

Table III—F Test to Determine the Number of Parameters Needed to Describe Chlorzoxazone Data Obtained for a Subject

	Number of Parameters in Model	Remaining Degrees of Freedom	Total Sum of Weighted Squared Deviations
	4	16 − 4 = 12	1409.7
	5	16 − 5 = 11	135.9
Difference	1	1	1273.8

$$F = \frac{1273.8}{135.9} \times \frac{11}{1} = 103.10^{a}$$

$$0.05\,F^{1}_{11} = 4.84$$

[a] Observed F exceeds critical F at 0.05 level of significance; therefore, the number of parameters should be increased from 4 to 5.

The plasma chlorzoxazone concentration and urinary excretion rate data of 6-hydroxychlorzoxazone glucuronide (as chlorzoxazone equivalents) for each individual subject were then simultaneously fitted by the least-squares method to Eqs. 1 and 2 using NONLIN (9) and a digital computer[7] to obtain estimates for the parameters V/f, K, k_a, k_{m2}, and k_{u2}. The mean plasma and urine data were also similarly fitted to Eqs. 1 and 2.

The least-squares estimates for one subject resulted in poor correlation owing to nonconvergence of the parameter k_a; hence, this subject was not included in the calculation of the average values. The average values for 22 subjects along with the parameter values obtained by simultaneous fitting of the mean plasma concentration–time data and the mean urinary excretion data are listed in Table II with the elimination half-life and plasma clearance values. There was good agreement between the average values for 22 subjects and the values obtained using the mean plasma concentration–time data. Average elimination half-life was 1.12 ± 0.48 hr and the average plasma clearance was 148.0 ± 39.9 ml/min. These values agree very well with the elimination half-life of 1 hr and the plasma clearance of 159.7 ml/min derived from the mean data. Figure 2 shows the model-predicted plasma concentration–time curve and the rate of excretion *versus* time at the midpoint of the urine collection period (t-MID) plot for one subject. Figure 3 shows the predicted curves for the mean plasma concentration–time data and the mean rate of excretion *versus* time (t-MID) plot. From these curves, it can be seen that excellent fits were obtained for the observed data when fitted to Eqs. 1 and 2 and that the scatter of the observed data about the theoretical curves was randomly distributed.

Equation 2 describes the rate of excretion of 6-hydroxychlorzoxazone glucuronide and is composed of the exponentials of three parameters: (*a*) the absorption rate constant of chlorzoxazone, (*b*) the elimination rate constant of chlorzoxazone, and (*c*) the excretion rate constant of the glucuronide. To test whether a three-exponential equation was needed, the data were fitted to a model consisting of the exponentials of only two parameters:

$$\underset{(\text{at } t = 0)}{fX_0} \xrightarrow{k_a} X \xrightarrow{k_{m1}} X_{1Gu}$$

Scheme III

which uses:

$$\frac{dX_{1Gu}}{dt} = k_{m1}X = \frac{k_{m1}k_a f X_0}{(k_a - K)}\left[e^{-Kt} - e^{-k_a t}\right] \qquad \text{(Eq. 3)}$$

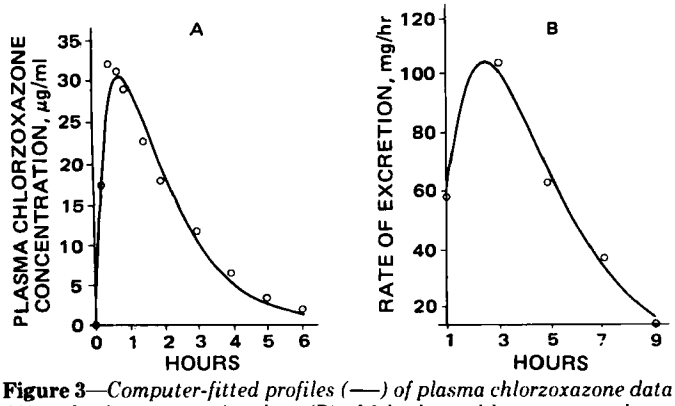


Figure 3—*Computer-fitted profiles (—) of plasma chlorzoxazone data (A) and urinary excretion data (B) of 6-hydroxychlorzoxazone glucuronide as chlorzoxazone equivalents obtained from the mean data. Circles represent observed means.*

[7] DEC 1099; Digital Equipment Corp.

Equation 3 resembles Eq. 1, *i.e.*, the rate of excretion of the glucuronide can also be described by only two exponentials, that describing absorption and that describing the overall elimination of the unchanged drug. The combined plasma and urine data were then fitted to Eqs. 1 and 3, and the parameters V/f, K, k_a, and k_{m1} were obtained.

As suggested by Boxenbaum *et al.* (10), an F ratio test was utilized to determine if it was justified to use four parameters instead of the original five to describe the data. Table III lists the number of parameters, the degrees of freedom, and the total sum of weighted, squared deviations obtained by fitting the combined plasma and urine data of one representative subject using four and five parameters. The results of the F test are also included and show that the observed F of 103.1 exceeds the critical F of 4.84, thereby suggesting that a minimum of five parameters are needed to define the data. Use of four parameters generally resulted in a relatively poor fit of the data and in higher values of total sum of weighted, squared deviations for all subjects and for the mean data. Application of Akaike's information criterion (11) confirmed the results of the F test, thus providing a strong justification for the use of five parameters instead of four.

A comparison of the least-squares estimates of the parameters V/f, K, k_a, k_{m1}, and k_{u2} (Table II) obtained by averaging the values for individual subjects and those obtained from the evaluation of the mean data showed a better correlation among the plasma parameters (V/f, K, and k_a) than among the urinary excretion rate parameters (k_{m1} and k_{u2}). This is probably because the urinary excretion data were described by only five samples, each obtained at intervals of 2 hr while plasma data were described by a minimum of 11 data points for each subject. This may have contributed to the variability observed in the urinary excretion parameters.

An apparent volume of distribution of ~ 14 liters (assuming complete systemic availability, $f = 1$) suggests that the drug is not widely distributed and that it would be confined to the circulatory system and possibly the extracellular fluid. Previous experiments (7) with dogs showed that the concentration of chlorzoxazone in the liver, muscle, brain, and kidney was approximately one-half or less that found in plasma. Chlorzoxazone concentration in fat was, however, twice that in plasma.

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