According to the data presented, Figs. 2 and 3 suggest that as the particles increase in size, the *in vivo* dissolution rate decreases such that the particles are removed from the conjunctival sac before dissolution is completed. Therefore, both the rate and the extent of penetration into aqueous humor are decreased.

It is possible that as particle size increases, a potential for discomfort is created. As a consequence, tearing could be induced and a progressively decreasing residence time might occur. No clear distinction has been made regarding an upper limit in particle size that would be considered comfortable and, therefore, would not induce tearing. Sieg and Robinson (2) stated that the particle size should be <10 μm to minimize particle irritation in the eye. However, shape and concentration are additional factors that make it difficult to select a specific particle size above which irritation or discomfort might result. From observing the animals during the study, there was no reason to believe that dexamethasone induced tearing at a concentration of 0.1% and an average size of 5.75–22 μm. Nevertheless, the present data do not rule out this possibility.

A potential source of variability between ophthalmic suspensions with different particle sizes could be differences in the amount of the administered dose. Table I lists the volume number diameter, d_{vn}, from which the number of particles per dose can be calculated. In low-strength suspensions such as 0.1% dexamethasone, as the drug particle size increases the number of particles per dose falls rapidly (*i.e.*, inversely with the cube of d_{vn}), potentially increasing the standard deviation of the drug concentration in a randomized dose. The last column in Table I illustrates this point.

Although a limited number of animals was used in the study, the results suggest that ophthalmic dexamethasone suspensions can be optimized for bioavailability by using suspensions with particles as small as possible. This approach would promote a rapid dissolution rate and reduce the chance of tearing and, therefore, would minimize rapid drainage as well as the variability in the quantity of dose administered.

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Pharmacokinetics and Bioavailability of Cimetidine in Humans

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Received August 28, 1979, from the **Department of Pharmacy, School of Pharmacy, and the* ‡*Division of Clinical Pharmacology, Department of Medicine, University of California, San Francisco, CA 94143.* Accepted for publication October 18, 1979. §Present address: Department of Pharmacology, University of Potchefstroom, Potchefstroom 2520, South Africa.

Abstract □ Cimetidine given orally without food after an overnight fast produces a blood concentration curve with a pronounced second peak that does not appear after parenteral administration or when the drug is taken with food. The following interpretation of this kinetic phenomenon is proposed: 1. The drug cumulates in a tissue or organ that is well perfused in the first-pass transfer. 2. The hepatic parenchymal tissue and the bile phase are the most likely storage areas. 3. The high capacity of the cumulation may be due to the formation of conjugates or other modifications of the drug with a pronounced affinity for the hepatic–biliary system. 4. The rate of cumulation is much higher in the first-pass transfer than from the systemic circulation, possibly due to the difference in the drug concentrations and the conjugation rate. 5. The cumulation appears to occur by a competitive process. 6. Absorbed elements of food seem to compete in this process. 7. The second peak apparently is the result of a rapid release of drug and bioreversible drug compounds from the hepatic–biliary system with subsequent reabsorption. 8. This release may occur spontaneously but appears to be triggered by food intake. A pharmacokinetic model constructed according to this interpretation showed good agreement with data from oral, intravenous, and intramuscular administration. The special problems associated with the evaluation of bioavailability in the presence of reabsorption are discussed.

Keyphrases □ Cimetidine—pharmacokinetics, bioavailability, humans □ Pharmacokinetics—cimetidine, humans □ Bioavailability—cimetidine, humans

Blood levels of cimetidine in humans after oral dosing (1–8) and intravenous administration (2, 5, 6) have been analyzed with respect to the pharmacological response (2), influence of a meal on absorption (3), biliary distribution and secretion (4), and bioavailability (1, 5, 6). The drug shows unusual pharmacokinetic behavior in producing a significant secondary peak in the drug concentration profile after oral dosing on a fasting stomach but not after intravenous administration (5–7). No attempts have been made to describe the pharmacokinetics of the phenomenon.

A conventional two-exponential model has been applied (6), but such a model does not account for the secondary peaks. Bodemar *et al.* (8) stated that: "A second absorption peak could be explained by enterohepatic circulation of cimetidine, although a preliminary report by Spence *et al.* (4) seems almost to exclude this possibility." Considering the possibility of delayed absorption of some of the cimetidine or a varying absorption rate at different segments of the GI tract (6), the same authors (1) stated that: "Calculations from the present results indicate that the consideration from a hypothetical delayed absorption is as much as 50% of total *AUC* in some patients. Delayed absorption of this magnitude, however, is unlikely and this second peak following oral administration of cimetidine remains to be explained."

This study was intended to evaluate the pharmacokinetics of cimetidine and to explain its kinetic discrepancy using the data of Walkenstein *et al.* (5). It is proposed that the phenomenon can be described best in terms of discontinuous reabsorption. The special problems associated with the evaluation of bioavailability in the presence of reabsorption are discussed.

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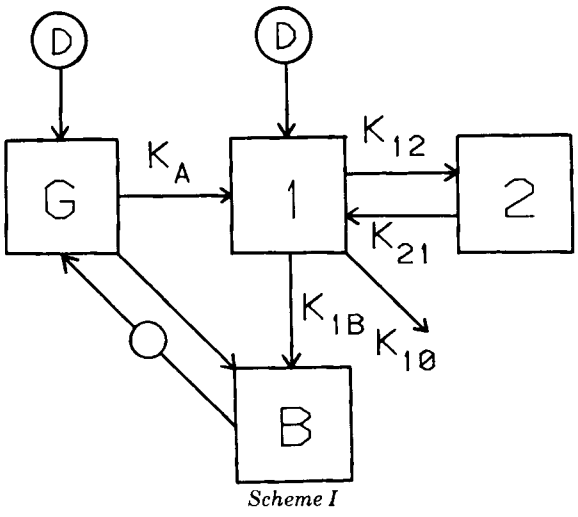

Scheme I

THEORY

The proposed pharmacokinetic model (Scheme I) was developed considering the reported kinetic behavior of cimetidine and encompasses the kinetics after oral, intravenous, and intramuscular administration.

Oral Administration—The drug is presented into the absorption compartment, G (the gut), where a fraction, F_{G1}, of the dose, D, is absorbed by a first-order process into the central, sampleable compartment, 1. The remaining fraction, $1 - F_{G1}$, of the drug goes into a compartment, B, in the first-pass transfer process. No assumptions are made about the type of transfer process from G to B because the kinetic behavior of the system does not depend on the rate of input into B but only on the amount of drug in B at a particular time, T_B. At this time, a fraction, F_B, of the drug cumulated in B is released momentarily into the absorption compartment.

The first-pass elimination reported for cimetidine (5, 6) is incorporated into $1 - F_{G1}$ for simplification. The drug is eliminated from the central compartment and transferred into compartment B and a peripheral compartment, 2, by first-order processes.

Intravenous and Intramuscular Administration—It has been shown that there are no significant differences in the blood level profiles between intravenous and intramuscular administration (5). The absorption from an intramuscular injection appears so rapidly that kinetically it can be considered as an intravenous administration. Therefore, the same model was applied for the two administrations. It is the same model as discussed, except that the input is a bolus input into the central compartment.

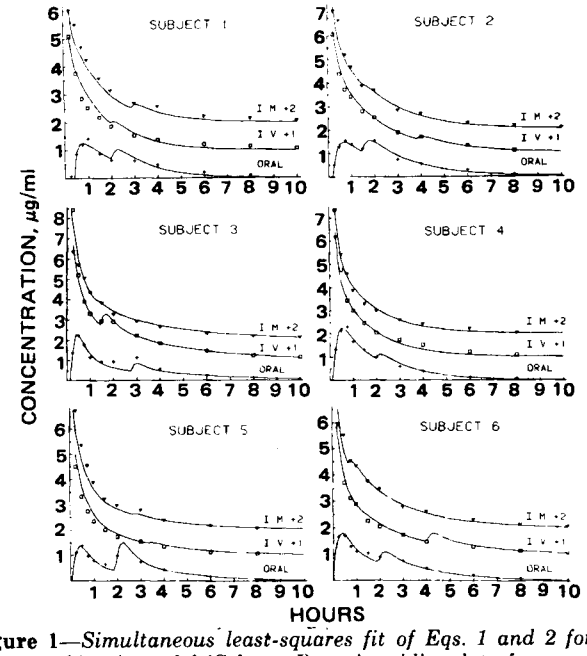

Figure 1—*Simultaneous least-squares fit of Eqs. 1 and 2 for the pharmacokinetic model (Scheme I) to cimetidine data from oral, intravenous, and intramuscular administration. The curves and data are staggered vertically one unit for clarity.*

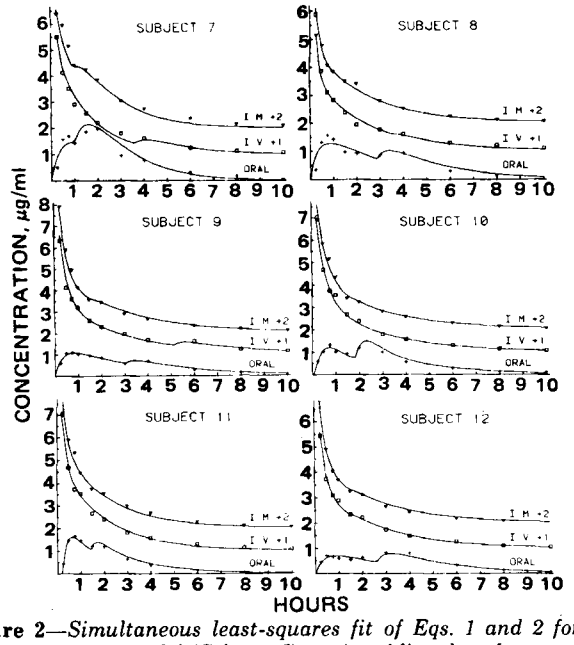

Figure 2—*Simultaneous least-squares fit of Eqs. 1 and 2 for the pharmacokinetic model (Scheme I) to cimetidine data from oral, intravenous, and intramuscular administration. The curves and data are staggered vertically one unit for clarity.*

The differences in the response profiles with respect to the presence or the absence of the secondary peak from an oral or parenteral administration is accounted for by the relative magnitude of the transfer rate of the drug from G to B and from 1 to B. A significant G to B transfer gives rise to a pronounced secondary peak. However, a slow 1 to B transfer, competing with elimination and distribution, results in only a small drug cumulation in B and an insignificant secondary peak, which may be difficult to detect in the blood level data (Figs. 1 and 2).

The choice of a discontinuous cyclic transfer process in the model is justified from physiological considerations (9, 10). Theoretical as well as simulation studies also indicate that secondary peaks cannot be obtained from linear compartmental systems with continuous cyclic transfer processes (11, 12).

Regression Equations—The following response equations are readily derived by standard means (13). After intravenous and intramuscular administration:

$$c = \frac{D}{V}[a_1e^{-\lambda_1 t} + a_2e^{-\lambda_2 t}] + \frac{K_A F_B D_B}{V}[a_3e^{-K_A(t-T_B)+} - a_4e^{-\lambda_1(t-T_B)+} - a_5e^{-\lambda_2(t-T_B)+}] \quad \text{(Eq. 1)}$$

and after oral administration:

$$c = \frac{K_A}{V}[F_{G1}D(a_3e^{-K_A(t-T_L)+} - a_4e^{-\lambda_1(t-T_L)+} - a_5e^{-\lambda_2(t-T_L)+}) + F_B D_B(a_3e^{-K_A(t-T_B)+} - a_4e^{-\lambda_1(t-T_B)+} - a_5e^{-\lambda_2(t-T_B)+})] \quad \text{(Eq. 2)}$$

where:

$$a_1 = (K_{21} - \lambda_1)/(\lambda_2 - \lambda_1) \quad \text{(Eq. 3)}$$

$$a_2 = (K_{21} - \lambda_2)/(\lambda_1 - \lambda_2) \quad \text{(Eq. 4)}$$

$$a_3 = (K_{21} - K_A)/(\lambda_1 - K_A)(\lambda_2 - K_A) \quad \text{(Eq. 5)}$$

$$a_4 = (K_{21} - \lambda_1)/(\lambda_1 - K_A)(\lambda_2 - \lambda_1) \quad \text{(Eq. 6)}$$

$$a_5 = (K_{21} - \lambda_2)/(\lambda_2 - K_A)(\lambda_1 - \lambda_2) \quad \text{(Eq. 7)}$$

and where after intravenous and intramuscular administration:

$$D_B = K_{1B}D\left[\frac{a_1}{\lambda_1}(1 - e^{-\lambda_1 T_B}) + \frac{a_2}{\lambda_2}(1 - e^{-\lambda_2 T_B})\right] \quad \text{(Eq. 8)}$$

while after oral administration:

$$D_B = X_B + (1 - F_{G1})D \quad \text{(Eq. 9)}$$

Table I—Least-Squares Parameter Estimates

Parameter	Subject 1	2	3	4	5	6	7	8	9	10	11	12	Mean (*CV*, %)
T_L	0.41	0.19	0.18	0.15	0.10	0.04	0.00	0.03	0.00	0.13	0.21	0.02	0.12 (99)
T_B (iv), hr	2.00	3.81	1.47	3.42	3.34	4.01	3.58	3.52	5.13	0.93	0.80	1.41	2.78 (50)
T_B (im), hr	2.88	1.51	1.25	1.25	2.70	0.65	0.96	0.75	1.50	1.51	0.45	1.50	1.41 (53)
T_B (po), hr	2.04	1.46	2.76	1.96	1.93	1.94	1.00	2.90	3.00	1.82	1.44	2.60	2.07 (30)
K_A, hr^{-1}	2.24	2.80	7.75	2.59	6.22	3.68	1.21	1.22	1.04	1.91	2.81	0.95	2.87 (74)
K_{12}, hr^{-1}	7.12	1.42	0.92	2.27	0.69	2.02	1.50	2.32	1.41	0.90	1.86	1.70	2.01 (84)
K_{21}, hr^{-1}	3.20	2.24	0.84	2.09	0.96	1.77	3.15	1.91	1.15	0.91	1.95	1.40	1.80 (45)
K_{1B}, hr^{-1}	0.95	0.19	0.44	0.0003	0.06	0.65	0.67	0.16	0.81	0.08	0.11	0.32	0.37 (88)
K_{el}, hr^{-1}	2.75	0.92	0.82	1.56	0.95	1.17	1.03	1.08	1.01	0.95	1.13	1.18	1.21 (43)
F_{G1}	0.37	0.39	0.41	0.57	0.37	0.48	0.62	0.62	0.44	0.36	0.39	0.36	0.45 (22)
F_B (iv)	0.21	0.27	0.50	0.21	0.42	0.21	0.20	0.27	0.13	0.64	0.19	0.34	0.30 (51)
F_B (im)	0.20	0.28	0.10	0.20	0.40	0.61	0.80	0.30	0.12	0.43	0.19	0.32	0.33 (63)
F_B (po)	0.20	0.28	0.10	0.20	0.50	0.20	0.80	0.50	0.12	0.44	0.20	0.32	0.32 (63)
V, liters	15.7	35.2	35.0	25.3	51.2	33.9	40.0	36.2	31.0	34.7	28.5	34.6	33.5 (25)

where:

$$X_B = K_{1B}K_AF_{G1}D\left[\frac{a_3}{K_A}(1 - e^{-K_A(T_B-T_L)}) - \frac{a_4}{\lambda_1}(1 - e^{-\lambda_1(T_B-T_L)}) - \frac{a_5}{\lambda_2}(1 - e^{-\lambda_2(T_B-T_L)})\right] \quad \text{(Eq. 10)}$$

The truncation function used in Eqs. 1 and 2 is defined by:

$$(x)_+ = \max(0,x) \quad \text{(Eq. 11)}$$

Data Treatment[1]—With the interactive program FUNFIT (14), Eqs. 1 and 2 were fitted simultaneously by nonlinear least-squares regression to the oral, intravenous, and intramuscular data for each of the 12 subjects (5). All estimated microparameters are common for the functions describing the intravenous, intramuscular, and oral data except for the time, T_B, and the fraction, F_B, of drug release from B (Table I).

RESULTS AND DISCUSSION

To elucidate the unusual kinetic behavior of cimetidine, it is appropriate to summarize the most pertinent findings in the literature:

F1. Cimetidine taken orally without food after an overnight fast produces a pronounced secondary peak in most subjects (1, 5).

F2. The secondary peak does not seem to be present when the drug is taken orally with food (1).

F3. Intravenous and intramuscular administrations of cimetidine do not result in secondary peaks as occur after oral administration (1, 5).

F4. With food, the initial rise in plasma cimetidine concentration appears more slowly than if the drug is taken without food on a fasting stomach (1, 3).

F5. Mean blood levels after equal doses of cimetidine given orally or parenterally do not differ significantly after 4 hr (5, 6).

F6. The drug appears to be completely and rapidly absorbed in the therapeutic dosing range after oral administration (1, 5).

F7. The extent of absorption apparently does not differ when the drug is administered on a fasting stomach with or without food (1).

F8. The bioavailability of the drug after oral administration is ~70% of the intravenous bioavailability. The reduction appears to be due to a first-pass effect rather than a drug release rate-limited absorption (1, 5).

F9. The *AUC* appears to be proportional to the oral dose in the therapeutic dosing range (1, 6).

F10. Cimetidine is eliminated mainly *via* the kidneys (2). An average of 0.75 of the drug is recovered unchanged in the urine after parenteral administration, while only 0.5 of it is recovered after oral administration (5).

F11. A small amount of material derived from cimetidine is excreted in the feces after intravenous administration of radiolabeled drug (6).

F12. The fecal radioactivity accounts for an average of 10% of orally administered labeled cimetidine regardless of the dose (400 or 800 mg) (6).

F13. An average of 70% of the radioactivity administered is recovered in the urine of healthy human subjects after an oral dose of 200 mg of labeled cimetidine.

F14. The concentration of cimetidine is approximately five times higher in the bile than in the blood of patients undergoing exploratory surgery of the common bile duct (4).

F15. The conjugation reaction is of considerable significance for the biliary excretion of a drug since it produces a substrate with particularly suitable properties for the hepatic system (15–17).

F16. Several isolated studies on the fate of orally administered conjugates indicate that they are reabsorbed largely after hydrolysis in the gut and that this step is important in relation to the enterohepatic cycle (15, 17, 18).

F17. Substances showing a bile–blood concentration ratio substantially larger than one appear to be transferred into the bile across the parenchymal cell wall by an active transport process (4, 15).

F18. Substances actively transferred by the liver cells compete for transport across the hepatic membrane into the bile (15, 19–22).

F19. Many compounds secreted in the bile have a marked affinity for localizing in hepatic parenchymal tissue (22–24).

F20. The gallbladder releases most of its bile content into the duodenum shortly after the intake of a meal, particularly when the meal is eaten on a fasting stomach (9, 10).

F21. The release of bile into the duodenum stimulates the flow of pancreatic juice (25).

F22. Spontaneous contractions of the gallbladder occur in the fasting stage (9).

F23. The volume difference between a full and contracted gallbladder is ~30–50 cm^3 (9).

F24. It takes the gallbladder 1.5–2 hr to fill after a full contraction (9).

F25. Cimetidine results in marked inhibition of both gastric acid and pepsin secretion (2).

Kinetic Interpretation—In studying the cimetidine data from intravenous, intramuscular, and oral administrations (1, 5) together with the described findings, the following interpretation of this drug's unusual kinetic behavior was reached:

1. The secondary peak appears to be due to a rapid release from a drug depot. The depot is located in a tissue or organ that is well perfused by the drug in the first-pass transfer. The bile and the hepatic parenchymal tissues are the most likely primary storage areas (F11, F14, F15, F19, and F20) (26).

2. The time for the release appears to coincide with the intake of food in most cases. The 2-hr interval between oral drug intake and breakfast agrees well with the start of the second peak (Figs. 1 and 2). The mean value of T_B is 2.1 hr (Table I) (F20 and F22).

3. Drug transfer into the depot occurs mainly in the first-pass process (F1 and F3).

4. This transfer is significantly inhibited, possibly by the way of competitive active membrane transport, when the drug is taken with food (F2, F17, and F18). The excretion of bile in response to food also may play a role if the smaller amount of bile in the hepatic system reduces the uptake rate or capacity of the system.

5. The transfer rate of drug into the depot from the systemic circulation is slow compared to the first-pass transfer (F1 and F3). This effect possibly is due to a pronounced drug concentration difference at the depot site for the two administration routes. The drug concentration is large in the first-pass perfusion of the depot organ before the drug reaches the general systemic circulation. However, when the drug is introduced parenterally in the systemic circulation, a substantial dilution takes place before it reaches the depot organ. The higher metabolic activity at the first-pass route also may contribute to a larger uptake of drug by the

[1] The figures were drawn by a Tektronix 4662 penplotter controlled by an IBM 370/145 computer.

Table II—Pharmacokinetic Parameters

Parameter	Subject 1	2	3	4	5	6	7	8	9	10	11	12	Mean (*CV*, %)
$t_{1/2}$, hr	0.98	1.37	2.28	1.13	1.67	1.51	1.08	1.64	1.92	1.92	1.40	1.70	1.55 (25)
AUC (iv), μg/ml/hr	7.35	9.73	11.85	7.60	6.32	8.35	8.13	7.89	10.49	9.31	9.38	7.74	8.68 (18)
AUC (im), μg/ml/hr	7.39	9.59	10.69	7.60	6.31	7.91	9.18	7.77	10.14	9.27	9.36	7.73	8.58 (15)
AUC (po), μ/ml/hr	3.57	5.32	5.06	5.01	4.29	4.67	7.30	6.41	5.13	5.86	4.84	4.27	5.14 (20)
D (iv)/ *AUC* (iv), liters/hr	40.8	30.8	25.3	39.5	47.5	35.9	36.9	38.0	28.6	32.2	32.0	38.7	35.5 (17)
D (im)/ *AUC* (im), liters/hr	40.6	31.3	28.1	39.5	47.6	37.9	32.7	38.6	29.6	32.5	32.0	38.8	35.8 (16)
D_T[a]/ *AUC* (po), liters/hr	43.1	32.4	28.8	39.5	48.5	39.6	41.3	39.3	31.2	33.0	32.2	40.8	37.5 (16)
$V \cdot K_{el}$, liters/hr	43.1	32.4	28.8	39.5	48.5	39.6	41.3	39.3	31.2	33.0	32.2	40.8	37.5 (16)
AUC (po)/ *AUC* (iv)	0.49	0.55	0.43	0.66	0.68	0.56	0.90	0.83	0.49	0.63	0.52	0.55	0.61 (23)
AUC (po)/ *AUC* (im)	0.48	0.56	0.47	0.66	0.68	0.59	0.80	0.81	0.51	0.63	0.52	0.55	0.64 (24)
D_T[a]/ *D* (po)	0.51	0.57	0.49	0.66	0.69	0.62	1.00	0.84	0.53	0.65	0.52	0.58	0.64 (24)

[a] $D_T = FD$ (po) + $F_B D_b$ (po).

depot (F8, F15, and F16).

6. Cimetidine possibly is stored in the depot both in the parent form and as conjugates or complexes. The large capacity of the hepatic system for storage and biliary excretion of conjugates may explain the magnitude of the secondary peak (F15 and F16).

Capacity of Hepatic System for Recycling—The theory of enterohepatic recycling to explain the second peak phenomenon has been criticized mainly because of the magnitude of the peak relative to the concentration of cimetidine found in the bile (4) and the estimated amount of bile secreted by the hepatic system into the intestine (9). However, it is difficult to evaluate the mechanism and capacity of the hepatic system for drug recycling. Data obtained with chronic biliary fistulas or with draining T-tubes after cholecystectomy may have to be interpreted with caution because of the inevitable loss of bile salts (27). In addition, liver disease in humans is a collection of functional and structural disabilities including inflammatory, neoplastic, and degenerative disorders in which the parenchyma, the biliary tree, and the vascular supply may be substantially affected (28, 29). Therefore, the disease state of the patient would play a significant role in the biliary excretion of the drug.

The studies of biliary secretion of cimetidine involved patients undergoing exploratory surgery of the common bile duct (4). Presumably, the patients did not have a normal hepatic–biliary function. The surgery seems to have had a pronounced effect on the pharmacokinetics since the peak venous concentration of cimetidine often differed by more than 100% in the same individual during the study. In contrast, the nonoperative studies involving healthy subjects showed a remarkably small intraindividual variation in the blood drug levels (1, 5). The concentration of cimetidine in the bile found in the operative study (4) apparently was based on an assay that considers only free, untransformed drugs (3). Conjugates or other modifications that may be present in high concentrations (F15) and may be responsible for a significant recycling (F16) apparently were not included.

Pharmacokinetic Model—The pharmacokinetic model proposed (Scheme I) is a highly simplified functional model constructed according to the given interpretation. The *B* compartment represents the depot of the drug that is partly released, F_B, at some time, T_B, soon after or during a meal or spontaneously before a meal (F22). The model appears to agree well with the data (Figs. 1 and 2) and shows that the transfer of the drug into *B* in the first pass (*G* to *B*) is primarily responsible for the cumulation of the drug in *B* while the systemic transfer (1 to *B*) only plays a minor role (Figs. 1 and 2 and Table I).

The least-squares estimate of T_B after oral administration is 2.1 hr, which is not significantly different from the time (2 hr) for the intake of food after oral drug administration (F20). Although it is difficult to detect a secondary peak or hump in the data from the parenteral administrations, nonlinear regression analysis indicates a small degree of recycling in some cases (Figs. 1 and 2). However, due to the sparseness and limited accuracy of the data, it is difficult to determine T_B and the magnitude of the recycling effect after parenteral administration. This situation is reflected in the coefficients of variation of the T_B values; they are approximately the same for intravenous and intramuscular administrations but significantly larger than those for oral administration (Table I).

Bioavailability—An interesting aspect of the recycling phenomenon is its influence on the *AUC* values and the interpretation of bioavailability calculations based on comparisons of such values. The ratio between *AUC* values in such cases cannot be used as a relative measure of the extent of drug absorption since the *AUC* is dependent on the extent of recycling. Therefore, the *AUC* does not properly reflect the extent of primary absorption. Thus, the evaluation of the extent of first-pass effect and the evaluation of bioequivalency of oral drug delivery systems are complicated using the model-independent *AUC* approach, so other techniques may be worth considering. However, the *AUC* still is a useful parameter since, physiologically and pharmacologically, it is a more meaningful parameter than a parameter that measures the extent of primary absorption.

By using the intravenous and intramuscular administrations as reference dosage forms and the integrated form of the regression equations to calculate the *AUC* values, the bioavailability of the oral dosage was 0.61 in both cases (Table II). This value corresponds well to the reported values of 0.62 and 0.59 obtained by log-linear trapezoidal integration (5).

It is evident that in the presence of recycling it is not possible to calculate *F*, the fraction of the dose given that reaches the systemic circulation, by a model-independent approach. With the present model, *F* can be calculated according to:

$$F = (F_{G1}D + F_B D_B)/D \qquad \text{(Eq. 12)}$$

The mean value of 0.64 obtained in this way (Table II) agrees with the quantities of drug and drug metabolites found in the urine and the feces (F10, F12, and F13).

The oral data showing the pronounced secondary peak were from an oral administration taken on a fasting stomach without food. Two hours was allowed to pass before food intake. Other investigations indicated that the second peak will not be present when cimetidine is taken orally with food (1). It has been recommended that cimetidine be taken with food to obtain the best therapeutic effect. Thus, the second peak seems to be an artifact from the experimental design and may not be of much significance in the practical therapeutic setting. This result raises the question of how appropriate it is to fast a subject before and during a pharmacokinetic study. It may not be appropriate if the objective is to estimate the normal pharmacokinetic behavior of a population or to provide practical guidelines for dosage regimens.

However, the particular experimental design does reveal an interesting pharmacokinetic phenomenon that may be of significance in organ and

tissue specific drug delivery, chemotherapy, and treatment of inflammatory and infectious diseases of the liver and biliary system.

NOTATIONS

$AUC = \int_0^\infty c\,dt$
B = drug depot compartment
c = blood cimetidine concentration
D = dose
$D_B = X_B + (1 - F_{G1})D$
$D_T = F_{G1}D + F_BD_B$, the apparent amount of the dose absorbed
$F = (F_{G1}D + F_BD_B)/D$, the apparent fraction of the dose absorbed
F_B = fraction of drug cumulated in B that is released to G at time $t = T_B$
F_{G1} = fraction of D absorbed by first-order absorption into the central compartment
$1 - F_{G1}$ = fraction of D transferred from G to B
G = compartment from which absorption takes place
K_{xx} = first-order transfer rate constants
$-\lambda_1, -\lambda_2$ = eigenvalues of the linear system
t = time
T_L = lag time
T_B = time when a part (F_BD_B) of the drug cumulated in B is released to G
V = volume of distribution
X_B = amount of drug transferred from compartment 1 to compartment B at time $t = T_B$

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Human Pharmacokinetics of a New Broad-Spectrum Parenteral Cephalosporin Antibiotic, Ceforanide

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Abstract □ The pharmacokinetics of the *l*-lysine salt of ceforanide were studied after intravenous administration of 1132 and 2264 mg as 30-min constant-rate infusions and after intramuscular administration of 556 and 1132 mg. The peak intravenous plasma concentrations were 136 and 222 μg/ml at termination of infusion, and 12-hr trough concentrations were 5.9 and 9.0 μg/ml, respectively. The peak intramuscular plasma concentrations were 38 and 74 μg/ml at 1.0–1.3 hr after dosing, and 12-hr trough concentrations were 3.9 and 6.7 μg/ml, respectively. When 19 successive intravenous and intramuscular doses at these levels were administered at 12-hr intervals, there was no tendency toward drug accumulation. The major drug elimination route was urinary excretion; 85% of the dose was excreted unchanged in the urine within 12 hr, and no metabolites with antibiotic activity were observed in urine. The mean terminal plasma half-life was 2.98 hr, the mean plasma protein binding was 80.6%, the steady-state volume of distribution was 12 liters, the plasma clearance was 45.9 ml/min/1.73 m^2, and the renal clearance was 34.9 ml/min/1.73 m^2. The pharmacokinetic properties and antibacterial activity spectrum indicate that this antibiotic should be effective in treating human bacterial infections when administered at 12-hr intervals. It is presently under clinical investigation.

Keyphrases □ Ceforanide—pharmacokinetics, humans □ Antibiotics, cephalosporins—ceforanide, pharmacokinetics, humans □ Pharmacokinetics, humans—ceforanide

The *in vitro* antimicrobial activity and *in vivo* properties in rodents of ceforanide, 7-[*o*-(aminomethyl)phenylacetamido]-3-[[[1-(carboxymethyl)-1*H*-tetrazol-5-yl]thio]methyl]-3-cephem-4-carboxylic acid, a new parenterally

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