Pharmacokinetics and Bioavailability of Ranitidine in Humans

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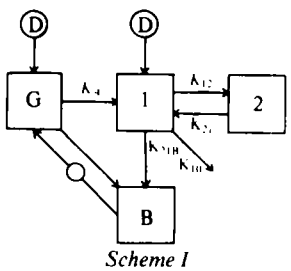
Abstract □ Ranitidine produces a blood concentration curve with a pronounced secondary peak when administered orally and parenterally. A pharmacokinetic model is proposed to describe this reabsorption phenomenon. The choice of a discontinuous cyclic transfer was justified on the basis of physiological considerations and the good agreement with data from oral and intravenous administration. It is proposed that ranitidine accumulates mainly from the systemic circulation into a depot from which drug and bioreversible drug are spontaneously released in response to food intake. The evaluation of the extent of the first-pass effect and the evaluation of bioequivalency are complicated by the model-independent AUC approach because the area under the concentration *versus* time curve (AUC) is dependent on the extent of recycling and thus does not properly reflect the extent of primary absorption. By using intravenous administration as a reference dosage form and the integrated form of the regression equations to calculate the AUC values, the bioavailability of the oral dose was found to be 0.56, which corresponds well with the value of 0.58 obtained by linear-log-linear integration. The least-squares parameter estimate of the primary absorption is 0.43.

Keyphrases □ Pharmacokinetics—bioavailability, ranitidine, humans □ Bioavailability—pharmacokinetics of ranitidine, humans □ Ranitidine—pharmacokinetics, bioavailability, humans

Evidence suggests that ranitidine, a new H_2-receptor antagonist, is at least five times more potent (on a molar basis) than cimetidine in inhibiting gastric acid secretion (1–3). Ranitidine shows unusual pharmacokinetic behavior by producing a significant secondary peak in the drug concentration profile after both oral dosing on a fasting stomach and intravenous administration (4). Cimetidine displays similar pharmacokinetic behavior after oral dosing on a fasting stomach but not after intravenous administration (5–7). Previous workers have concluded that a model requiring two exponential terms did not adequately describe ranitidine plasma level data after oral or intravenous administration (4). It is the purpose of this study to evaluate the pharmacokinetics of ranitidine with the data of Woodings *et al.* (4)[1]. It is proposed that ranitidine pharmacokinetics can be described by a two-compartment model and that the secondary peaks observed in the plasma level data can be described best in terms of discontinuous reabsorption.

EXPERIMENTAL SECTION

Theory—The proposed model (Scheme I) encompasses the kinetics of ranitidine after oral and intravenous administration (8). After oral administration, the drug is presented into the gut, the absorption compartment (G), from which a fraction (F_{G1}) of the dose (D) is absorbed by a first-order process into the central compartment (1) from which samples may be obtained. The remaining fraction ($1 - F_{G1}$) of the drug passes into 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 the time that recycling takes place. At this time (t_B), a fraction (F_B) of the drug accumulated in B is spontaneously released into the absorption compartment. The drug is eliminated from the central compartment and transferred into compartment B and a peripheral compartment (2) by first-order processes. After intravenous administration, the same model applies, except that the input is a bolus input into the central compartment.



Scheme I

The choice of a discontinuous cyclic transfer process in the model is based on theoretical as well as simulation studies, which indicate that secondary peaks cannot be obtained from linear compartmental systems with continuous cyclic transfer processes (9, 10).

Data Treatment—By using the nonlinear regression program NONLIN (11), the equations describing this model (8) were fitted simultaneously by nonlinear least-squares regression to the intravenous and oral data for each of the six subjects at each dosage level. The data set for subject 1 (dose, 80 mg) was excluded from analysis since intravenous data were not available. The blood sample obtained 2 min after intravenous administration was excluded

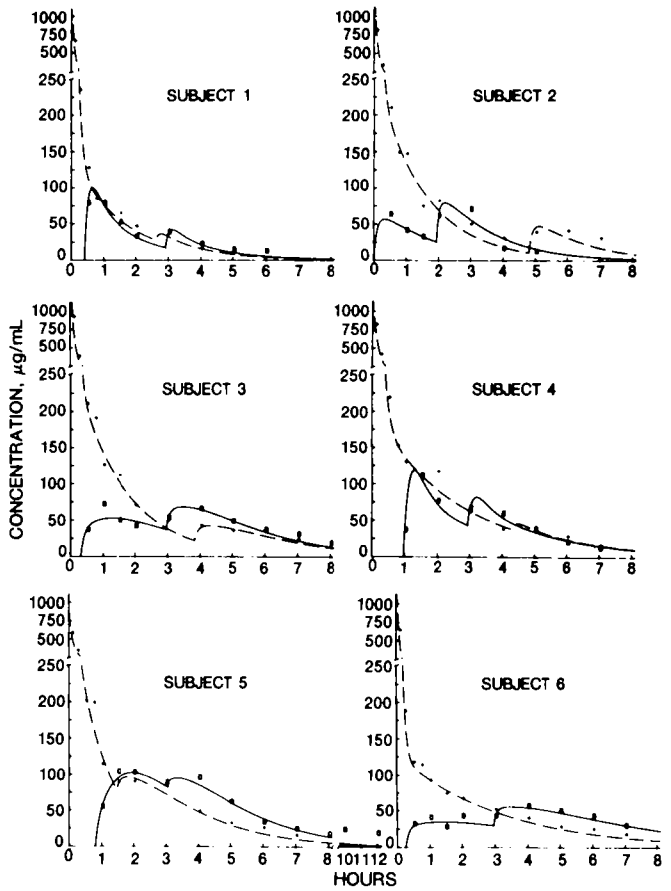


Figure 1—*Simultaneous least-squares fit of appropriate equations (8) for the pharmacokinetic model* (Scheme I) *to ranitidine data from oral (——) and intravenous (- - -) administrations of 20 mg of ranitidine.*

[1] Glaxo-Allenbury's Research (Ware) Ltd., personal communication.

0022-3549/84/1000-1376$01.00/0

Table I—Least-Squares Parameter Estimates

Parameter	Subject (Dose, mg)																		
	1(20)	1(40)	2(20)	2(40)	2(80)	3(20)	3(40)	3(80)	4(20)	4(40)	4(80)	5(20)	5(40)	5(80)	6(20)	6(40)	6(80)	Mean	*CV*, %
t_L, h	0.40	0.98	0.00	0.00	0.00	0.31	0.38	0.40	0.97	0.33	0.41	0.81	0.00	0.00	0.27	0.00	0.49	0.34	98
t_B (i.v.), h	2.61	3.90	4.80	2.72	3.81	3.82	3.03	1.30	4.27	0.52	1.36	1.46	1.55	3.95	0.37	1.92	0.50	2.46	59
t_B (p.o.), h	2.91	3.00	1.93	3.98	1.49	2.94	2.67	2.03	2.93	1.32	1.48	2.98	1.26	1.45	2.96	2.88	2.86	2.42	33
k_A, h^{-1}	2.44	1.76	1.82	0.64	1.00	0.65	0.52	0.33	2.45	0.59	0.38	0.56	0.95	2.99	0.61	0.35	0.38	1.08	80
k_{12}, h^{-1}	4.45	6.01	5.82	2.95	4.29	5.54	8.88	2.93	3.54	18.75	5.70	4.22	2.07	5.89	8.13	3.17	6.66	5.82	65
k_{21}, h^{-1}	1.62	2.13	2.31	1.57	1.18	2.18	1.53	2.22	1.35	2.89	4.12	4.63	1.58	1.91	1.37	1.21	2.58	2.14	46
k_{1B}, h^{-1}	3.49	1.40	1.68	2.14	4.81	2.56	1.65	11.32	0.92	21.46	14.62	11.94	3.70	4.30	0.20	20.30	13.31	7.05	99
k_{el}, h^{-1}	3.45	2.57	2.99	2.16	2.90	3.09	3.22	2.57	1.80	11.10	4.28	2.24	1.09	2.02	2.91	3.01	3.25	3.21	67
F_{GI}	0.43	0.40	0.23	0.77	0.16	0.36	0.26	0.42	0.38	0.28	0.65	0.93	0.42	0.32	0.39	0.33	0.62	0.43	46
F_B (i.v.)	0.06	0.23	0.29	0.25	0.04	0.25	0.27	0.20	0.08	0.39	0.19	0.12	0.01	0.17	0.01	0.04	0.39	0.18	71
F_B (p.o.)	0.13	0.25	0.28	0.27	0.20	0.33	0.21	0.16	0.19	0.25	0.63	0.10	0.54	0.21	0.55	0.29	0.26	0.29	53
V, L	16.8	19.2	12.9	29.2	12.9	11.5	8.9	20.1	16.4	3.3	11.7	22.4	36.2	22.0	13.6	20.2	18.4	17.4	44

from data analysis since at this time the drug was apparently not completely mixed in the blood. The intravenous data were, therefore, treated as a bolus administration with plasma concentrations obtained after 5 min.

RESULTS

All estimated microparameters are common for the functions describing the intravenous and oral data except for the time t_B and the fraction F_{BI} of drug release from B (Table I). The results are summarized in Tables I and II and Figs. 1–3. The conventional two-compartment model (12) fitted to the data in the same way as described above performed consistently poorer, as judged by the information criterion of Akaike (13).

The secondary peak in the plasma concentration–time curves after ranitidine administration (Figs. 1–3) appears to be due to a rapid release of ranitidine from a drug depot. The bile and hepatic parenchymal tissues are the most likely primary storage areas (14–16). The time for the release appears to coincide with the intake of food in most cases and is intermediate between the time when free fluids were permitted, 2 h after administration of ranitidine, and the time when a light lunch was provided, 3 h after administration[1]. The mean value of t_B after intravenous administration is 2.5 h, and after oral administration is 2.4 h (Table I).

The transfer of drug into the depot occurs after both oral and intravenous administration of ranitidine since a pronounced secondary peak can be observed after either form of administration. Cimetidine, on the other hand, shows a pronounced secondary peak only after oral administration (5–7). The transfer rate of cimetidine into the depot from the systemic circulation is slow compared with the first-pass transfer (8). The transfer of ranitidine into the depot, however, appears to be mainly from the systemic circulation. The mean transfer of ranitidine from the systemic circulation into the depot is 7.05 h^{-1} (Table I), which is 19 times more rapid than that of cimetidine (0.37 h^{-1}), as determined in a different group of subjects using the same model as in Scheme I (8). The area under the concentration *versus* time curve (AUC) due to ranitidine recycling was calculated by integrating the second half of the regression equations (8). The mean AUC due to recycling, normalized for dose, after intravenous and oral administration is 5.33 $ng \cdot mL^{-1} \cdot h^{-1} \cdot mg^{-1}$ (*CV* 86%) and 6.03 $ng \cdot mL^{-1} \cdot h^{-1} \cdot mg^{-1}$ (*CV*, 44%), respectively. The larger AUC after oral administration may indicate that a certain amount of ranitidine is transferred to the depot during the first-pass transfer. The difference, however, is not statistically significant.

DISCUSSION

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. Spontaneous contractions of the gallbladder have been shown to occur in the fasting stage (17). The secondary peak in the plasma concentration–time curves after ranitidine administration (Figs. 1–3) could be explained by enterohepatic circulation of ranitidine, but no information with respect to concentrations of ranitidine in bile is presently available in humans. Biliary accumulation studies in anesthetized rats showed that, in this species, up to 17% of an intravenous dose was excreted in the bile during 4–5 h (14). The model appears to agree well with the data (Figs. 1–3) and shows that the transfer of the drug into compartment B from systemic circulation (1 to B) is primarily responsible for the accumulation of the drug in B, whereas the transfer of the drug into B in the first pass (G to B) only plays a minor role (Figs. 1–3, Table I). Secondary peaks are evident but not pronounced if ranitidine is taken with food (18). The excretion of bile in response to food may play a role if the smaller amount of bile in the hepatic system reduces the uptake rate or capacity of the system.

An interesting aspect of the recycling phenomenon is its influence on the AUC values and the interpretation of bioavailability. The ratio between AUC values cannot be used as a relative measure of the extent of the drug absorption since the AUC is dependent on the extent of recycling. The AUC, therefore, does not properly reflect the extent of primary absorption (F_{GI}). By using the intravenous administration as a reference dosage form and the integrated form of the regression equations to calculate the AUC values, the bioavailability (F) of the oral dosage was 0.56 (Table II). The value obtained by linear trapezoidal integration is 0.49 (4). The linear trapezoidal method is particularly suitable when area estimates are to be compared among data which have similar shapes and sampling schemes; however, in cases in which changes in curvature between data points are excessive or there are long intervals between data points, large algorithm errors are known to occur (11, 19). No single numerical integration procedure presently available can be used to achieve maximal accuracy over all regions of the plasma concentration *versus* time curve. The best approach at present appears to be the use of the spline method during the absorption phase followed by the log-linear trapezoidal method

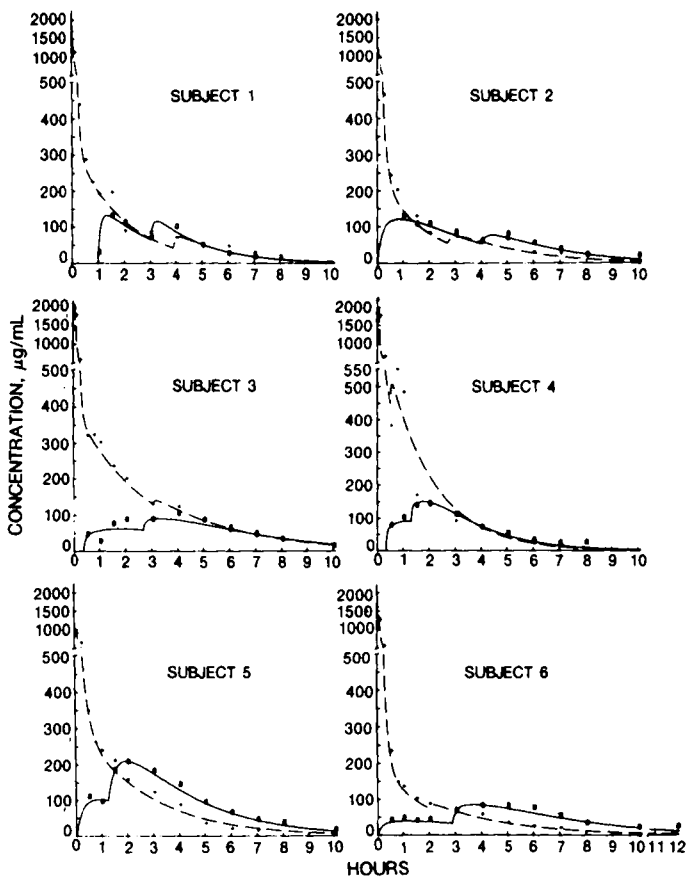


Figure 2—*Simultaneus least-squares fit of appropriate equations (8) for the pharmacokineteic model* (Scheme I) *to ranitidine data from oral (——) and intravenous (- - -) administrations of 40 mg of ranitidine.*

Table II—Pharmacokinetic Parameters

Parameter	Subject (Dose, mg)																	Mean	*CV*, %
	1(20)	1(40)	2(20)	2(40)	2(80)	3(20)	3(40)	3(80)	4(20)	4(40)	4(80)	5(20)	5(40)	5(80)	6(20)	6(40)	6(80)		
$t_{1/2}$, h	1.1	1.29	1.05	1.26	1.61	1.05	1.87	0.83	1.82	0.69	0.50	0.67	1.73	1.69	2.1	1.3	0.98	1.27	37
Vd_{ss}, L	63.2	73.7	45.5	84.0	59.7	40.7	60.4	46.5	59.6	24.7	27.8	42.7	83.7	89.9	94.2	73.1	66.0	60.9	34
AUC (i.v.), ng·h/mL	361.6	897.5	598.9	763.5	2274.7	674.6	1538.6	2608.6	701.0	1591.4	2267.7	610.1	1030.1	2332.6	505.7	782.6	2323.0	—[c]	—[c]
AUC (po), ng·h/mL	188.8	471.8	243.8	627.3	747.6	358.6	603.8	907.8	353.8	548.2	1686.2	478.9	948.0	948.6	369.8	543.8	1305.4	—[c]	—[c]
D (i.v.)/AUC (i.v.), L/h	55.3	44.6	33.4	52.4	35.2	29.6	26.0	30.7	28.5	25.1	35.2	32.8	38.8	34.3	39.5	51.1	34.4	36.9	25
D (i.v.)/AUC$_t$, L/L[a]	58.1	49.6	38.7	63.2	37.3	35.4	28.6	51.4	29.5	36.6	53.9	50.0	39.4	44.5	39.6	60.7	59.9	45.7	24
D_t/AUC (po), L/h[b]	58.2	49.5	38.5	62.9	37.4	35.1	28.1	51.8	29.3	36.1	54.2	49.6	39.2	44.7	39.6	60.4	60.2	45.6	25
Vk_{et}, L/h	58.0	49.3	38.6	63.1	37.4	35.5	28.7	51.7	29.5	36.6	50.1	50.2	39.5	44.4	39.6	60.8	59.8	45.5	24
AUC (po)/AUC (i.v.)	0.52	0.53	0.41	0.82	0.33	0.53	0.39	0.35	0.50	0.34	0.74	0.78	0.92	0.41	0.73	0.69	0.56	0.56	33
D_t/D (po)[b]	0.55	0.58	0.47	0.99	0.35	0.63	0.42	0.59	0.52	0.49	1.14	1.19	0.93	0.53	0.73	0.82	0.98	0.70	37

[a] AUC_t = AUC (i.v.) − $AUC_{(B)}$ where $AUC_{(B)}$ = area under curve resulting from recycling. [b] $D_t = FD(po) + F_BD_B(po)$. [c] The mean value is only applicable if normalized for dose.

during the elimination phase (20). However, since the computer program for the spline method is not generally available, the use of the linear trapezoidal method during the absorption phase and the log-linear trapezoidal method in the postabsorption phase is the most logical general approach. The linear-log-linear trapezoidal combination has the advantage that it is simple to apply and yields very acceptable results (21).

The AUC after intravenous and oral administration was calculated by the linear trapezoidal method for the ascending portions of the curve, whereas the log-linear trapezoidal method was used during the descending parts of the curve. The AUC was extrapolated to infinity by using the least-squares-fitted terminal log-linear slope. The model-independent bioavailability of 0.58 (*CV* 35%) thus calculated corresponds very well to the value of 0.56 calculated from the model-dependent integrated form of the regression equations (Table II).

It is evident that in the presence of recycling it is not possible to calculate F_{G1} by a model-independent approach. With the present model, F_{G1} can be determined by the nonlinear least-squares regression to the intravenous and oral data. The mean value of 0.43 (Table I) corresponds well with the extent of cimetidine primary absorption of 0.45 (8). The AUC is still a useful parameter since, physiologically and pharmacologically, it is a more meaningful parameter than one which measures the extent of primary absorption. The extent of recycled drug, however, plays a large and varying role in the determination of total bioavailability. Those times at which accumulation of drug in the recycling compartment is mainly due to the first-pass effect the secondary peak would usually be observed mainly after oral administration, as is the case for cimetidine (4). Bioavailability calculated by using the AUC after intravenous administration as a reference, therefore, varies, depending on the extent of recycling after intravenous and oral administration. F may appear to be smaller than F_{G1} if recycling after intravenous administration is greater, similar to F_{G1} if the extent of recycling is similar after intravenous and oral administration, and greater than F_{G1} if the extent of recycling after oral administration is greater. This phenomenon can be illustrated by comparing F (Table II) and F_{G1} (Table I) in subject 5. After the 40-mg dose, the secondary peak was negligible after intravenous administration and relatively large after oral administration (Fig. 2). This is reflected by a relatively large F of 0.92, as compared with the F_{G1} of 0.42. After the 80-mg dose, the secondary peaks appear to be equally large after intravenous and oral administration (Fig. 3). This is reflected by a value for F of 0.41 which is still larger than but very similar to the F_{G1} of 0.32. After the 20-mg dose, the secondary peaks after intravenous and oral administration are not very extensive and appear to be similar. The value of 0.78 for F, however, is now smaller than 0.93 for F_{G1}, which reflects more extensive recycling after intravenous administration. For ranitidine, F is generally larger than F_{G1}, except for subject 3 (80-mg dose), subject 5 (20-mg dose), and subject 6 (80-mg dose) in which the opposite is true (Tables I and II). The bioavailability of ranitidine (0.56) is lower than that of cimetidine (0.61), although the extent of primary absorption is very similar (8). This may simply be an artifact of the method of calculating bioavailability, since the greater AUC after intravenous administration of ranitidine due to recycling may artificially reduce this value.

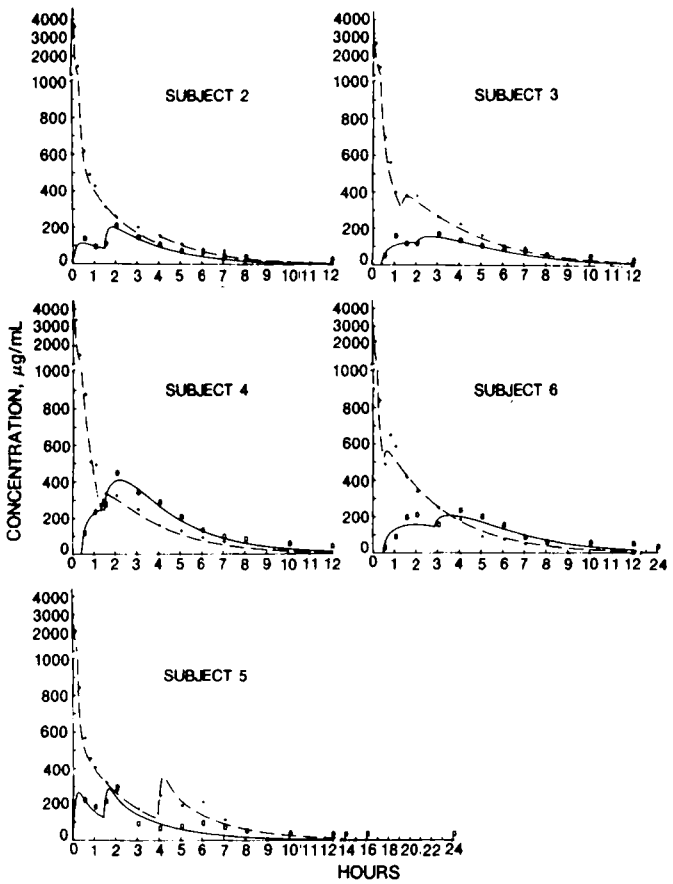


Figure 3—*Simultaneous least-squares fit of appropriate equations (8) for the pharmacokinetic model* (Scheme I) *to ranitidine data from oral (——) and intravenous (- - -) administrations of 80 mg of ranitidine.*

Ranitidine clearance, calculated as the ratio of the dose to AUC after intravenous administration, is 36.9 L/h (Table II), which is similar to cimetidine clearance, which is 35.5 L/h (8). If the AUC is corrected for recycling, the clearance of ranitidine is 45.7 L/h (Table II). Recycling of ranitidine, therefore, apparently decreases the clearance of ranitidine by ~20%. The lower clearance parameter is pharmacokinetically more meaningful and relates to the average plasma concentration attained with any particular dose.

The major difference in the pharmacokinetics of ranitidine and cimetidine appears to be that recycled ranitidine is accumulated mainly from the systemic circulation, whereas accumulation of cimetidine takes place mainly during first-pass transfer. This may be due to high affinity of ranitidine from the systemic circulation for bile. The secondary peak, however, does not seem to be present when cimetidine is taken orally with food (22), and the same phenomenon may occur after intravenous administration. The excretion of bile in response to food may play a role if the smaller amount of bile in the hepatic system reduces the uptake rate or capacity of the system. In this case, neglecting to adhere strictly to the oral administration fasting protocol when administering the drug intravenously could result in secondary peaks that are greatly reduced or absent. Under these circumstances, the assumption that cimetidine is accumulated mainly during the first-pass transfer would not be valid. To avoid any ambiguity, the identical protocol should be followed when the drug is administered extravascularly and intravascularly. In any event, this difference, whether real or spurious, would probably not account for the large difference in potency.

GLOSSARY

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 = AUC_{po}/AUC_{iv}, the apparent fraction of the dose absorbed
F_B = fraction of drug accumulated 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_{ZZ} = first-order transfer rate constants
t = time
t_L = lag time
t_B = time when a part (F_BD_B) of the drug accumulated in B is released to G
Vd = volume of distribution
X_B = amount of drug transferred from compartment 1 to compartment B at time $t = t_B$

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ACKNOWLEDGMENTS

This work was supported by the South African Research Council.

Dose-Dependent Pharmacokinetic Study of Pefloxacin, A New Antibacterial Agent, in Humans

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Received June 29, 1983 from the *Laboratoire de Biochimie I et de Pharmacologie, Centre Hospitalier Intercommunal de Créteil, 94010 Créteil Cedex, France.* Accepted for publication September 26, 1983.

Abstract □ A dose-dependent pharmacokinetic study of pefloxacin was performed after four intravenous infusions and four orally administered doses. After intravenous infusion, the pharmacokinetic profiles of the plasma concentrations showed a biphasic decline, with half-lives (mean ± *SD*) of 8.55 ± 4.20 min and 11.50 ± 1.75 h, respectively. Intravenous infusion and oral administration yielded similar results. The pharmacokinetic parameters remained constant in the dose range of 200–800 mg from the plasma and urine data.

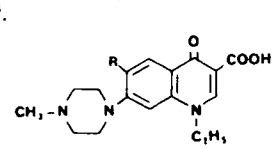
Keyphrases □ Pharmacokinetics—dose-dependent, pefloxacin, new antibacterial agent □ Pefloxacin—new antibacterial agent, dose-dependent pharmacokinetics □ Antibacterial agent—dose-dependent pharmacokinetics of pefloxacin

Pefloxacin[1], 1-ethyl-6-fluoro-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid (I), is a new antibacterial compound shown to be highly active against both Gram-negative and Gram-positive bacteria (1, 2). A large percentage (85%) of the drug administered is transformed into several metabolites, the *N*-oxide, the demethyl, and the oxodemethyl analogues (3). Since the pharmacokinetic data for this drug have not been reported in humans, a preliminary study was performed to investigate the plasma and urine profiles of pefloxacin in a dose-dependency study in humans.

EXPERIMENTAL SECTION

Materials—Pefloxacin and its 6-chloro analogue[1] (II) (the internal standard) showed no impurities in two different TLC systems. All reagents were commercially available analytical grades and used without further purification.

Pefloxacin Analysis—Unchanged pefloxacin in plasma or urine was measured by HPLC (3) using a liquid chromatograph[2] equipped with a UV spectrophotometer (280 nm) and a continuous flow cell with an 8-μL capacity. A 200-mm steel column was used, packed with a monomolecular layer of octadecyltrichlorosilane chemically bonded to silica beads with an average particle size of 7 μm[3].



I: R = F
II: R = Cl

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0022-3549/84/1000-1379$01.00/0