Use of a Pharmacokinetic Model Incorporating Discontinuous Gastrointestinal Absorption to Examine the Occurrence of Double Peaks in Oral Concentration–Time Profiles[1]

A. Benjamin Suttle,[2] Gary M. Pollack,[2] and Kim L. R. Brouwer[2,3]

Received February 12, 1991; accepted September 10, 1991

Double peaks in the plasma concentration–time profile following oral administration have been reported for several compounds. A pharmacokinetic model incorporating discontinuous absorption was developed to simulate concentration–time profiles with double peaks. The gastrointestinal (GI) tract was divided into N compartments, with absorption occurring only from the second and Nth compartments. A two-compartment model was used to describe systemic drug disposition. The effect of gastric emptying and GI transit rate constants (K_1 and K_t, respectively), number of hypothetical gut compartments, and absorption rate constant at each site (K_{a1}, K_{a2}) on the time of occurrence of each peak (T_{p1}, T_{p2}), the theoretical fraction of the dose absorbed at each site (Φ_1, Φ_2), and the contribution of the second site to systemic drug exposure (expressed as Φ_{2rel}) were examined. Simulated concentration–time profiles demonstrated that T_{p2} was determined by K_t and N, while T_{p1} was determined by K_1 and K_t. Changes in K_{a1} and K_{a2} had no effect on T_{p1} or T_{p2}. Φ_1, Φ_2, and Φ_{2rel} were determined by K_{a1}, K_{a2}, and K_t, and simulations indicated that a secondary peak in the concentration–time profile will be evident only when Φ_{2rel} is substantial. In addition, concentration–time data for ranitidine and cimetidine, which displayed double peaks, were fit with the model. The present model described both data sets well, and realistic pharmacokinetic and physiologic parameters (absorption rate constants, systemic bioavailabilities, GI residence times) were obtained.

KEY WORDS: discontinuous gastrointestinal (GI) absorption; double peaks; H2-receptor antagonists.

INTRODUCTION

Distinct double peaks in the plasma concentration–time profile have been observed following oral administration of many compounds including ranitidine (1), cimetidine (2,3), furosemide (4), penicillamine (5), and veralipride (6). Delayed gastric emptying of a portion of an orally administered dose has been proposed as the mechanism responsible for double peaks in cimetidine concentration–time profiles (3) and the irregular concentration–time profile of ceftibuten (7). However, double peaks in the concentration–time profiles following direct administration of ranitidine into the duodenum and jejunum of human subjects (8) indicated that factors other than gastric emptying may be responsible for secondary peaks. Other possible mechanisms of the double-peaking phenomenon include enterohepatic recirculation, storage and subsequent release of drug from a postabsorptive depot site (possibly liver parenchymal cells) (9), variable absorption rates along the gastrointestinal (GI) tract (10,11), and discontinuous absorption (6).

Pharmacokinetic models have been developed previously to describe segmental absorption from the GI tract (3,11–14). These models were based on the assumption that absorption is continuous throughout a segment of the GI tract but that the rate of absorption varies as the administered drug moves through the gut. A limitation of these previous models is that they do not include nonabsorbing GI segments between the absorption sites and, therefore, are not models of discontinuous absorption *per se*. Plusquellec and others (6) proposed a pharmacokinetic model incorporating a nonabsorbing intestinal segment between two absorption sites. A limiting assumption of that model was that drug could not exist in the first and second absorption sites simultaneously. This assumption is not valid when the two absorption sites lie close together. Site-specific absorption in the GI tract has been demonstrated for several nutrients (15) and suggested for other drugs (16,17). It is conceivable that site-specific absorption may occur at more than one region within the GI tract.

The present study was undertaken to develop a pharmacokinetic model incorporating discontinuous absorption along the GI tract that can reproduce double peaks in simulated concentration–time profiles. A secondary goal of the study was to determine the influence of various model parameters (absorption rate constants, number of gut compartments, and gut compartment transfer rates) on the simulated concentration–time profiles. To this end, parameters in the model were altered systematically and the resulting effects on the simulated concentration–time profiles were determined. Finally, the ability of the model to describe systemic concentration–time data evidencing the double-peak phenomenon was tested with previously reported data for the H_2-receptor antagonists cimetidine and ranitidine.

THEORETICAL

For the purposes of modeling truly discontinuous absorption, it is assumed that two spatially separate absorption sites exist in the GI tract. Absorption does not take place in intervening regions between the two absorption sites and ceases when all drug exits the second absorption site. Therefore, as the mass of drug moves aborally through the gut, it will enter and exit both areas of the gut where absorption occurs. The rate of drug presentation to the first absorption site is dependent upon the administered dose and the drug transfer rate into the site. The rate of presentation to the second absorption site is dependent upon the efficiency of the first absorption site, the distance between the two ab-

[1] This work was presented in part at the 5th Annual Meeting of the American Association of Pharmaceutical Scientists, November 4–8, 1990, Las Vegas, Nevada.

[2] Division of Pharmaceutics, School of Pharmacy, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599.

[3] To whom correspondence should be addressed at Division of Pharmaceutics, School of Pharmacy CB 7360, Beard Hall, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-7360.

0724-8741/92/0300-0350$06.50/0

sorption sites, and the rate at which the drug traverses the nonabsorbing regions of the gut.

To develop a model of truly discontinuous absorption, the GI tract was assumed to behave as a catenary system of N distinct compartments. The present model included absorption of drug from only the second and terminal (Nth) gut compartments. Between absorption compartments, $N - 3$ intervening compartments were included. Drug was lost from a particular gut compartment through transfer to the adjacent distal gut compartment (compartments 1 to $N - 1$), absorption into the systemic circulation (from compartments 2 and N), and passage out of the terminus of the GI system (from gut compartment N).

Drug transfer from gut compartment 1 to gut compartment 2 was assigned a first-order rate constant (K_1) to provide a parameter analogous to a gastric emptying rate. One first-order rate constant (K_t) was used to describe drug transfer from each of compartments 2 through $N - 1$ to the adjacent distal compartment and from the Nth compartment out of the system. The first-order rate constants K_{a1} and K_{a2} determined absorption from the second and Nth gut compartments, respectively. A two-compartment model was used to describe the systemic disposition of the compound. Elimination from the central compartment was assumed to be first-order and was governed by the rate constant K_{10}. Intercompartmental transfer was determined by the first-order rate constants K_{12} and K_{21}. The model is depicted schematically in Fig. 1.

The equations comprising the model system were derived as their respective Laplace transforms. The disposition function for drug in the first gut compartment ($d_{s,1}$) was written as

$$d_{s,1} = \frac{1}{(s + K_1)} \tag{1}$$

where K_1 is the first-order rate constant for drug transfer from gut compartment 1 to gut compartment 2 and s is the Laplace operator. To incorporate a lag time (T_L) between administration of the dose and the time drug was available for transfer to gut compartment 2, input into the first gut compartment was described as a zero-order process beginning at time T_L. The zero-order input rate (K_0) was defined as delivery of the entire dose over a time period equal to 1% of T_L. The Laplace transform of the input function into gut compartment 1 ($i_{s,1}$) was written as

$$i_{s,1} = \int K_0 * e^{-st} \tag{2}$$

Integration of this expression from T_L to $1.01 * T_L$ yielded the square-wave input function:

$$i_{s,1} = \frac{K_0 * [e^{(-T_L * s)} - e^{(-1.01 * T_L * s)}]}{s} \tag{3}$$

The product of the input and disposition functions yielded the Laplace transform for drug flux through gut compartment 1, $L(X_1)$:

$$L(X_1) = \frac{K_0 * [e^{(-T_L * s)} - e^{(-1.01 * T_L * s)}]}{[s * (s + K_1)]} \tag{4}$$

For gut compartments containing no drug at time 0, the Laplace transform for drug flux through each compartment was written as the product of the rate constant entering the compartment and the Laplace transform for mass of drug in the preceding compartment divided by the sum of the rate constants exiting the compartment plus the Laplace operator s. The flux of drug through the remaining gut compartments was written as follows.

Drug in gut compartment 2:

$$L(X_2) = \frac{K_1 * L(X_1)}{(s + K_t + K_{a1})} \tag{5}$$

*Drug in intervening (nonabsorbing) gut compartments (*i = *3 through* N − *1):*

$$L(X_i) = \frac{K_t * L(X_{i-1})}{(s + K_t)} \tag{6}$$

*Drug in terminal (*N*th) gut compartment:*

$$L(X_N) = \frac{K_t * L(X_{N-1})}{(s + K_t + K_{a2})} \tag{7}$$

where $L(X_2)$, $L(X_{i-1})$, $L(X_i)$, $L(X_{N-1})$, and $L(X_N)$ represent the Laplace transforms for drug flux in gut compartments 2, $i - 1$, i, $N - 1$, and N, respectively.

When multiple intervening compartments were included in the model ($N > 3$), simplification of the Laplace transforms resulted in the following expression for the penultimate gut compartment:

$$L(X_{N-1}) = \frac{(K_t)^{N-3} * L(X_2)}{(s + K_t)^{N-3}} \tag{8}$$

where $N - 3$ is the number of nonabsorbing, intervening gut compartments present between the second and the Nth gut compartments.

The flux of drug through the central and peripheral compartments was described as follows.

Drug in central compartment:

$$L(X_C) = \frac{K_{a1} * L(X_2) + K_{a2} * L(X_N) + K_{21} * L(X_P)}{(s + K_{10} + K_{12})} \tag{9}$$

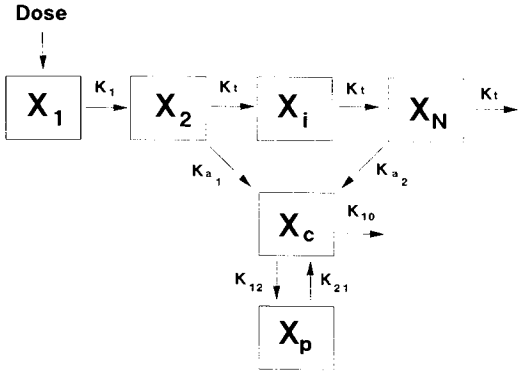

Fig. 1. Scheme of the model describing discontinuous absorption. See text for explanation of symbols.

Drug in peripheral compartment:

$$L(X_P) = \frac{K_{12} * L(X_C)}{(s + K_{21})} \quad (10)$$

where $L(X_C)$ and $L(X_P)$ are the Laplace transforms for drug mass in the central and peripheral compartments, respectively. Substitution of Eq. (10) into Eq. (9) yielded the final form of the Laplace transform of drug mass in the central compartment:

$$L(X_C) = \frac{[K_{a1} * L(X_2) + K_{a2} * L(X_N)] * (s + K_{21})}{[(s + K_{21}) * (s + K_{10} + K_{12})] - K_{21} * K_{12}} \quad (11)$$

Because concentration, as opposed to drug mass, is more relevant to pharmacokinetic modeling, $L(X_C)$ was divided by the volume of the central compartment (V_C) to produce the expression for flux of drug concentration through the central compartment.

METHODS

Ranitidine is a commonly prescribed drug that often exhibits double peaks in the concentration–time profile following oral administration. Therefore, systemic disposition parameters for ranitidine (18) were used in the present simulation study. Values for K_{a1}, K_{a2}, K_t, and T_L that produced double peaks of similar magnitude and time of occurrence as those reported in the literature were chosen for the initial simulation (see Table I).

Equation (11) was inverted to generate simulated concentration–time profiles with the computer software package Laplace (MicroMath, Inc., Salt Lake City, UT). All simulations were based upon a single dose of drug, with $t = 0$ representing the time of drug administration. Data points were generated at 24-min intervals from 0.1 to 5 hr and at 1-hr intervals from 5 to 12 hr. Individual pharmacokinetic parameters in the model were varied in each simulation to assess their influence on the concentration–time profile. The effects of changes in gastric emptying rate and GI transit rate were investigated by varying K_1 and K_t, respectively. The influence of the number of intervening compartments between absorption sites was examined by varying N. Changes in the efficiency of drug absorption at each absorption site were modeled by varying K_{a1} and K_{a2}.

The time of occurrence of each peak (T_{p1} and T_{p2}) and the maximum concentration of each peak (C_{max1} and C_{max2}) were determined by inspection of the concentration–time data for each simulation. The theoretical fraction of drug absorbed at the first and second absorption sites (Φ_1 and Φ_2, respectively) was calculated as the ratio of the absorption rate constant to the sum of all rate constants exiting the absorption compartment.

$$\Phi_1 = \frac{K_{a1}}{(K_t + K_{a1})} \quad (12)$$

$$\Phi_2 = \frac{(1 - \Phi_1) * K_{a2}}{(K_t + K_{a2})} \quad (13)$$

The theoretical contribution of the second absorption site to the total drug absorption (Φ_{2rel}) was calculated as

$$\Phi_{2rel} = \frac{\Phi_2}{(\Phi_1 + \Phi_2)} \quad (14)$$

To test the ability of the present pharmacokinetic model to estimate relevant pharmacokinetic parameters, the model was fit to ranitidine and cimetidine concentration–time data exhibiting double peaks. The parameters N, K_t, K_1, K_{a1}, K_{a2}, and T_L were varied to minimize the sum of squared errors for each fit. Ranitidine data were obtained from a concentration–time profile reported following a 100-mg oral dose to healthy volunteers (1). Concentration–time data following intravenous administration of ranitidine to the subject from whom the oral data were obtained were fit with a two-compartment model with RSTRIP (MicroMath, Inc., Salt Lake City, UT) to generate values of K_{12}, K_{21}, K_{10}, and V_C.

Cimetidine data following oral administration of a 400-mg tablet were provided kindly by Dr. Isadore Kanfer (personal communication) and fit with the present model. Values of K_{12}, K_{21}, K_{10}, and V_C for cimetidine were obtained by

Table I. Effects of Changes in Model Parameters[a]

Simulation	N	K_{a1} (hr^{-1})	K_{a2} (hr^{-1})	K_t (hr^{-1})	K_1 (hr^{-1})	T_{p1} (hr)	T_{p2} (hr)	Φ_1	Φ_2	Φ_{2rel} (%)
1	11	1.2	2	5	4	0.84	2.55	0.19	0.23	55
2	15	1.2	2	5	4	0.84	3.53	0.19	0.23	55
3	23	1.2	2	5	4	0.84	5	0.19	0.23	55
4	15	1.2	2	2.5	4	0.84	6	0.32	0.30	48
5	15	1.2	2	8	4	0.59	2.30	0.13	0.17	57
6	15	1.2	2	15	4	0.59	1.57	0.07	0.11	61
7	15	1.2	1.2	5	4	0.59	3.50	0.19	0.15	44
8	15	1.2	5	5	4	0.59	3.50	0.19	0.40	68
9	15	1.2	0.3	5	4	0.59	—[b]	0.19	0.05	21
10	15	5	1.2	5	4	0.59	—[b]	0.50	0.10	17
11	15	0.3	1.2	5	4	0.59	3.50	0.06	0.18	75
12	15	1.2	2	5	1	1.08	3.78	0.19	0.23	55
13	15	1.2	2	5	2	0.84	3.53	0.19	0.23	55
14	15	1.2	2	5	8	0.59	3.28	0.19	0.23	55

[a] $K_{12} = 2\ hr^{-1}$, $K_{21} = 1.5\ hr^{-1}$, $K_{10} = 1.5\ hr^{-1}$, $V_C = 27$ L, dose = 150 mg, and $T_L = 0.2$ hr during each simulation.

[b] No second peak evident.

fitting a two-compartment model to previously reported concentration–time data obtained following intravenous administration of cimetidine to healthy volunteers (2).

RESULTS

The pharmacokinetic data derived from all simulations are listed in Table I. The simulated concentration–time profiles produced when the total number of gut compartments was varied are presented in Fig. 2. In simulations where only N increased, T_{p2} increased and C_{max2} decreased, while T_{p1} and C_{max1} remained unchanged (Table I, simulations 1–3).

The effects of changes in K_t on the simulated concentration–time profiles are shown in Fig. 3. Larger values of K_t, and therefore decreased residence times of drug in each gut compartment, resulted in decreased T_{p2}, Φ_1, and Φ_2 values (Table I, simulations 4–6). Decreased residence times of drug in each gut compartment also resulted in a greater fraction of the dose escaping absorption from gut compartment 2 and reaching the second absorption site. Therefore, values of Φ_{2rel} increased when K_t increased.

The effects of changes in the efficiencies of each absorption process on systemic drug concentrations are displayed in Figs. 4 and 5. Varying only K_{a1} and K_{a2} had no influence on T_{p1} and T_{p2}, regardless of whether K_{a1} and K_{a2} were less than or greater than K_t (Table I, simulations 7–11). T_{p1} has a theoretical minimum determined by T_L and K_1 independent of changes in K_{a1} and K_t. Likewise, T_{p2} has a theoretical minimum determined predominantly by N and T_L as well as K_t. However, the maximum concentration of each peak was affected markedly by changes in K_{a1} and K_{a2}. When Φ_1 was approximately five times greater than Φ_2, no second peak was evident in the simulated concentration–time profile. Simulations indicated that a secondary peak in the concentration–time profile will be evident only when the second absorption site contributes a substantial fraction to the absorbed dose.

The effects of varying K_1 on the concentration–time profile are displayed in Fig. 6. Increasing K_1 from 1 to 8 hr^{-1} resulted in an approximately twofold decrease in T_{p1} and only a slight decrease in T_{p2} (Table I, simulations 12–14).

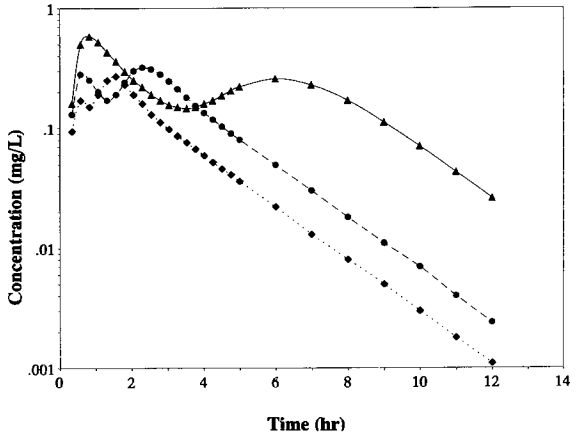

Fig. 3. Influence of K_t on concentration–time profiles. (▲——▲) K_t = 2.5 hr^{-1}; (●–●) K_t = 8 hr^{-1}; (◆--◆) K_t = 15 hr^{-1}. Other parameter values as in Table I.

Although K_1 did not influence Φ_1 or Φ_2, C_{max1} and C_{max2} increased as K_1 increased.

The concentration–time profiles after oral administration of ranitidine and cimetidine and the best fit of the model to those data are shown in Figs. 7 and 8, respectively. The parameters providing the best fit to each data set are listed in Table II. Because of the absence of cimetidine iv data, the micro rate constants used in fitting the model to the data were only estimates of the true constants in that subject. Therefore, the model overestimated concentrations in the terminal elimination phase of the profile.

DISCUSSION

Parameters related to factors involved in oral absorption (absorption rate constants, gastric emptying, gastrointestinal transit rates) were included in the present model. However, the model is a mathematical description of discontinuous GI absorption rather than a direct physiologic representation of the gut. The first gut compartment is analogous to the stomach, and compartments 2 through N represent hypothetical sites along the intestine, with no direct anatomical corre-

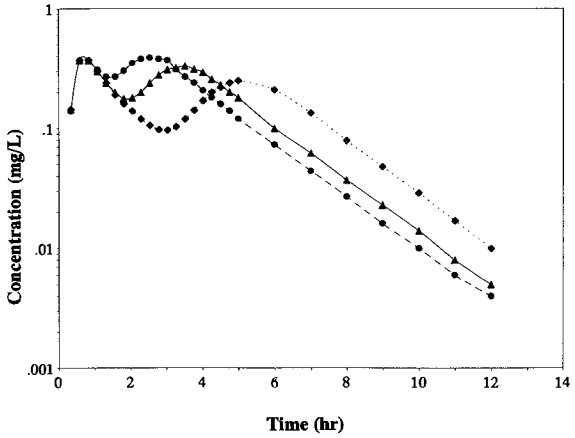

Fig. 2. Influence of N on concentration–time profiles. (●–●) N = 11; (▲——▲) N = 15; (◆--◆) N = 23. Other parameter values as in Table I.

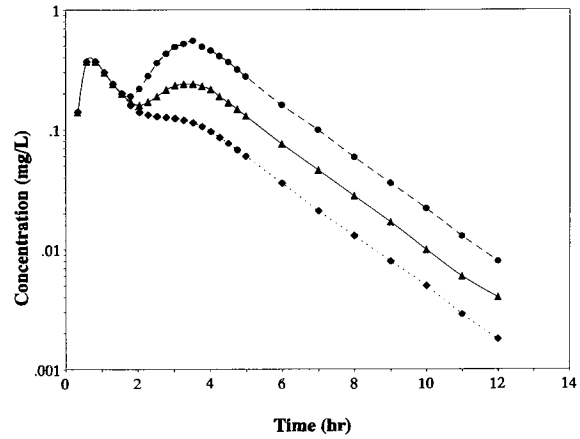

Fig. 4. Influence of K_{a1} and K_{a2} on concentration–time profiles. (▲——▲) Φ_1 = 0.19, Φ_2 = 0.15; (●–●) Φ_1 = 0.19, Φ_2 = 0.4; (◆--◆) Φ_1 = 0.19, Φ_2 = 0.05. Other parameter values as in Table I.

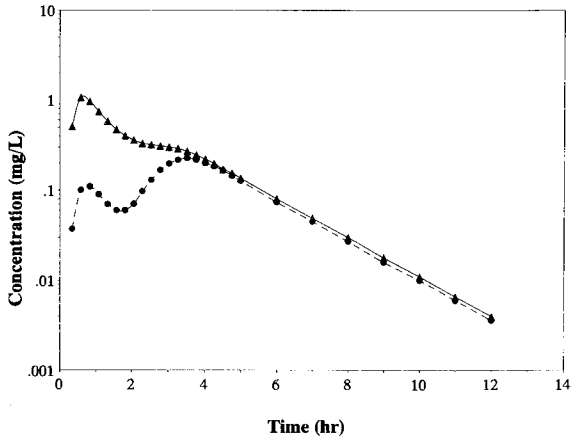

Fig. 5. Influence of K_{a1} and K_{a2} on concentration–time profiles (▲——▲) $\Phi_1 = 0.5$, $\Phi_2 = 0.1$; (●–●) $\Phi_1 = 0.06$, $\Phi_2 = 0.18$. Other parameter values as in Table I.

lates. Compartmental transfer rates are analogous to gastric emptying and intestinal motility rates. No assumptions concerning the size or volume of any gut compartment were made.

Gastric emptying has been shown to be a first-order process (19–21), suggesting that K_1 is an appropriate parameter for transfer of drug from gut compartment 1 to gut compartment 2. An assumption made in developing the present model was that the rate of intestinal transit remained constant throughout the gut. In contrast, GI motility *in vivo* varies with time and decreases in a stepwise fashion from the upper duodenum to the ileum (15). Therefore, K_t must be considered a first-order approximation of the overall GI transit rate.

The degree of separation between the two peaks in the concentration–time profiles was controlled primarily by the number of gut compartments in the model (N) and the compartmental transfer rate (K_t). N may be interpreted as being proportional to the distance between the two absorption sites; however, large values of N do not necessarily indicate that the two absorption sites are physically far removed from each other. Large values of N may suggest that the apparent

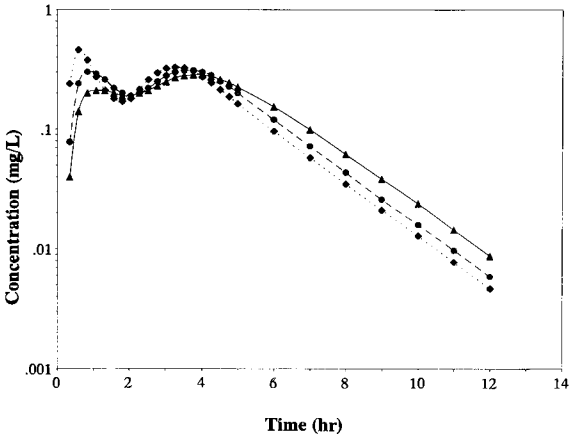

Fig. 6. Influence of K_1 on concentration–time profiles. (▲——▲) $K_1 = 1\ hr^{-1}$; (●–●) $K_1 = 2\ hr^{-1}$; (◆--◆) $K_1 = 8\ hr^{-1}$. Other parameter values as in Table I.

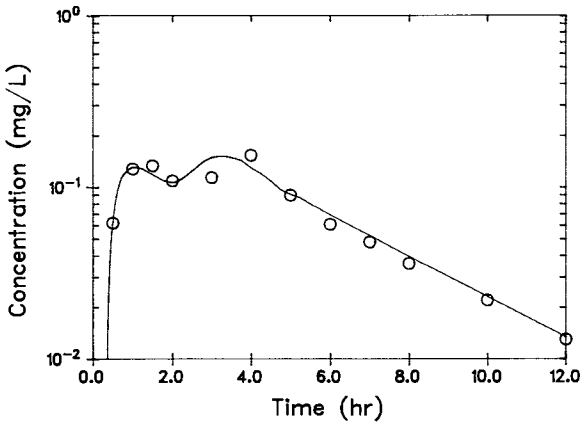

Fig. 7. Best fit of model to oral ranitidine concentration–time profile (parameter values as in Table II).

compartments in the gut are small, and drug molecules have a relatively short residence time in discrete gut regions. A relevant analogy to the latter situation is the influence of theoretical plate height on chromatographic separation. Simulations with large values of both N (and therefore small "theoretical plate heights") and K_t produced two well-defined and well-separated peaks.

A term for the number of gut compartments included in the model is incorporated in the Laplace transform for the penultimate gut compartment [Eq. (8)]. The exponent in that expression ($N - 3$) is equal to the number of nonabsorbing gut compartments between the two absorption sites. Therefore, one parameter (N) can be varied to observe the influence of multiple intervening compartments on the systemic concentration–time profiles without requiring the use of additional equations.

The present model adequately described the ranitidine and cimetidine data obtained in human volunteers and produced physiologically relevant parameter values. Single-site absorption rate constants reported for ranitidine and cimetidine range from 0.55 to 2.15 hr^{-1} (22) and 0.95 to 7.75 hr^{-1} (9), respectively. Values of K_{a1} yielding the best model fit for both ranitidine and cimetidine agreed with these ranges. Similarly, the bioavailability of ranitidine calculated from the best-fit parameters ($F = 0.45$) was in agreement with the

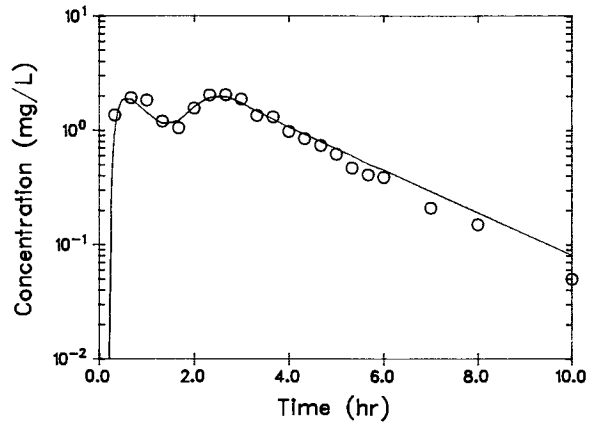

Fig. 8. Best fit of model to oral cimetidine concentration–time profile (parameter values as in Table II).

Table II. Best-Fit Parameters for Ranitidine and Cimetidine

	Ranitidine	Cimetidine
N	20	17
K_t (hr^{-1})	10	10
K_1 (hr^{-1})	1.5	5
T_L (hr)	0.3	0.25
K_{a1} (hr^{-1})	3.5	4.5
K_{a2} (hr^{-1})	4	8.5
K_{12} (hr^{-1})	1.425	2.37
K_{21} (hr^{-1})	0.96	2.05
K_{10} (hr^{-1})	0.836	1.06
V_C (L)	63	29

systemic bioavailability of 47% based upon iv and po AUC data (1). The percentage of the cimetidine dose absorbed calculated from the best-fit parameters (F = 0.63) also agreed well with the mean bioavailability of 62% reported in normal subjects (23).

To assess the physiologic relevance of the parameters N, K_1, and K_t, the mean residence time (MRT) of drug in each gut compartment was calculated as the sum of the reciprocals of the rate constants governing drug flux through each compartment. Since ranitidine (8) and cimetidine (24) are poorly absorbed from the colon, the region of the GI tract described by the present model corresponds to the small intestine and stomach. The reported gastric MRT of liquids typically ranges from 11.5 to 22 min (21). The MRT of ranitidine in the first gut compartment (MRT = 40 min) was somewhat longer than this range; the MRT of cimetidine in the first gut compartment (MRT = 12 min) was within this range. The sum of the MRTs in gut compartments 2 through N indicates the residence time of drug in the portion of the GI tract where the absorption sites are located. The MRT in gut compartments 2 through N calculated from the parameters yielding the best model fit to the data were 4.34 and 3.64 hr for ranitidine and cimetidine, respectively. Both results are well within the range of 3 to 5 hr (21) reported for transit time from the upper duodenum to the ileocecal junction in fasted subjects.

The appearance of double peaks in concentration–time profiles is dependent on the frequency of blood sample collection. Frequent blood sampling (every 20 min through 6 hr) resulted in well-characterized double peaks in the cimetidine concentration–time data presented. However, if blood samples are drawn less frequently, only one peak (or plateau) may be observed in the concentration–time profile. The present model may be useful in determining an appropriate sampling schedule to elucidate double peaks in concentration–time profiles following oral administration of a compound.

In summary, a pharmacokinetic model was developed to describe discontinuous absorption from the GI tract; the model was able to reproduce double peaks in simulated concentration–time profiles. Furthermore, the model produced realistic pharmacokinetic and physiologic parameters when fit to ranitidine and cimetidine concentration–time data, suggesting that the model was appropriate. Further experimentation is required to verify the hypothesis of discontinuous absorption and to determine the loci of the absorption sites in the GI tract.

ACKNOWLEDGMENT

This work was supported by a grant from ICI Americas, Inc.

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