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

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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 (K₁ and Kᵣ, respectively), number of hypothetical gut compartments, and absorption rate constant at each site (Kᵣ₁, Kᵣ₂) on the time of occurrence of each peak (Tᵢ₁, Tᵢ₂), the theoretical fraction of the dose absorbed at each site (Φᵢ, Φᵢ₂), and the contribution of the second site to systemic drug exposure (expressed as Φᵢ₂₉) were examined. Simulated concentration–time profiles demonstrated that Tᵢ₂ was determined by Kᵣ and N, while Tᵢ₁ was determined by Kᵣᵣ and Kᵣ₁. Changes in Kᵣ₁ and Kᵣ₂ had no effect on Tᵢ₁ or Tᵢ₂; Φᵢ₁, Φᵢ₂, and Φᵢ₂₉ were determined by Kᵣᵣ₁, Kᵣᵣ₂, and Kᵣᵣ₁, and simulations indicated that a secondary peak in the concentration–time profile will be evident only when Φᵢ₂₉ 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 bioavailability, GI residence times) were obtained.

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

INTRODUCTION

Distinctive 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 verapamil (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 cefitubuten (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-peak phenomenon include enterohemepatic 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. Plusquellic 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 H₂-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-
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 (\( K_i \)) to provide a parameter analogous to a gastric emptying rate. One first-order rate constant (\( K_i \)) 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

\[
d_{s,1} = \frac{1}{(s + K_1)}
\]

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 \( T_{1L} \) 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 \( T_{1L} \). The zero-order input rate \( (K_0) \) was defined as delivery of the entire dose over a time period equal to 1% of \( T_{1L} \). The Laplace transform of the input function into gut compartment 1 \( (i_{s,1}) \) was written as

\[
i_{s,1} = \int K_0 \cdot e^{-st} \,
\]

Integration of this expression from \( T_{1L} \) to 1.01 \( * T_{1L} \) yielded the square-wave input function:

\[
i_{s,1} = \frac{K_0 \cdot [e^{(-Ts_{1L})} - e^{(-1.01T_{1L}s_{1L})}]}{s} \quad (3)
\]

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

\[
L(X_1) = \frac{K_0 \cdot [e^{(-Ts_{1L})} - e^{(-1.01T_{1L}s_{1L})}]}{[s \cdot (s + K_1)]} \quad (4)
\]

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:**

\[
L(X_2) = \frac{K_1 \cdot L(X_1)}{(s + K_1 + K_{a1})} \quad (5)
\]

**Drug in intervening (nonabsorbing) gut compartments** \( (i = 3 \text{ through } N - 1) \):

\[
L(X_i) = \frac{K_i \cdot L(X_{i-1})}{(s + K_i)} \quad (6)
\]

**Drug in terminal (Nth) gut compartment:**

\[
L(X_N) = \frac{K_i \cdot L(X_{N-1})}{(s + K_i + K_{a2})} \quad (7)
\]

where \( L(X_2), L(X_{i-1}), L(X_n), L(X_{N-1}), \) 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:

\[
L(X_{N-1}) = \frac{(K_0)^{N-3} \cdot L(X_2)}{(s + K_0)^{N-3}} \quad (8)
\]

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:**

\[
L(X_C) = \frac{K_{a1} \cdot L(X_2) + K_{a2} \cdot L(X_N) + K_{21} \cdot L(X_{p})}{(s + K_{10} + K_{12})} \quad (9)
\]

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