Discontinuous Absorption Processes in Pharmacokinetic Models

RICHARD SÜVERKRÜP

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Abstract □ The limited contact time of absorbable drug with absorbing surfaces is, in some cases, a significant factor determining the fraction of the dose absorbed. A simple modification of customary linear compartmental models is presented to account for this situation, and a general input function in the Laplace domain for truncated first-order absorption is derived. An extension to series of truncated absorption processes is discussed.

Keyphrases □ Bioavailability—pharmacokinetic models, limited absorption time, fraction of dose absorbed □ Models, pharmacokinetic—bioavailability, limited absorption time, fraction of dose absorbed □ Drug absorption—pharmacokinetic models, limited absorption time

For clinical purposes, a detailed knowledge of intestinal and rectal drug absorption times from dosage forms is not essential. Information about the fraction of the dose entering the general circulation or available at the site of action, peak plasma levels and the times at which they occur, and the time range during which the minimum effective concentration is exceeded is all that is necessary for treating patients. However, in bioavailability assessment for dosage form development and some diagnostic purposes, details of absorption kinetics are important and approximation by an infinite first-order process is not always sufficient. A simple but flexible way to handle this problem in linear models is presented.

BACKGROUND

Kübler (1–3) worked out an intestinal absorption theory on the basic assumption that drug is absorbed from a columnar volume of chymus traveling down the gut, which is considered as a tube of finite length. His results on ascorbic acid absorption indicate that there may be several intestinal segments with different absorption efficiencies.

In the simplest case (one homogeneous absorption segment and a one-compartment open body model without drug degradation in the intestinal lumen, gut wall metabolism, and first-pass effect), four rather unhandy equations describe the plasma concentration–time course (*b*).

Let t_1 be the time when the column has completely entered the absorbing segment and let t_2 be the time when its front first reaches the end of this segment. With the assumptions that entry starts at $t = 0$, the column does not increase in length during passage, the transport rate is equal at entry and exit, and the column can be regarded as a well-stirred compartment, for the time interval $0 < t < t_1$:

$$b = \frac{D_0}{V_c k_1 t_1 (k_1 - k_2)} [k_1(1 - e^{-k_2 t}) - k_2(1 - e^{-k_1 t})] \quad \text{(Eq. 1)}$$

where V_c is the volume of the body compartment and k_1 and k_2 are the first-order rate constants of absorption and overall elimination, respectively. When $t_1 < t < t_2$, the whole length of the column is in contact with the absorbing surface and the plasma level function reads:

$$b = \frac{D_0}{V_c k_2 t_1 (k_1 - k_2)} [k_1 e^{-k_2 t}(e^{k_2 t_1} - 1) - k_2 e^{-k_1 t}(e^{k_1 t_1} - 1)] \quad \text{(Eq. 2)}$$

During exit, for $t_2 < t < t_1 + t_2$:

$$b = \frac{D_0}{V_c k_2 t_1 (k_1 - k_2)} \{k_1 e^{-k_2 t}[e^{k_2 t_1} + e^{-(k_1 - k_2)t_2} - 1] - k_2 e^{-k_1(t - t_1)} - (k_1 - k_2) e^{-k_1 t_2}\} \quad \text{(Eq. 3)}$$

Finally, when there is no more absorption going on at $t > t_1 + t_2$, the terminal phase is described by:

$$b = \frac{D_0}{V_c k_2 t_1 (k_1 - k_2)} k_1 e^{-k_2 t}(e^{k_2 t_1} - 1)[1 - e^{-(k_1 - k_2)t_2}] \quad \text{(Eq. 4)}$$

Although this approach is evidently better suited to describing the kinetics of first-order absorption than any model based on the assumption that the intestine behaves like a well-stirred compartment in which unabsorbed drug potentially resides indefinitely, there can be no doubt that the situation is really more complex.

Dilution occurs during intestinal passage, and there may be losses due to microbial or enzymatic degradation in the gut lumen as well as to intestinal wall metabolism. If the latter processes are linear, they are easily accounted for by introducing into Eqs. 1–4 a factor, f, defined as the quotient of the absorption rate constant for unchanged drug over the sum of all rate constants of parallel first-order processes removing drug from the absorption site. It is this sum that appears as k_1 in Eqs. 1–4.

Dilution may be worth more consideration. During intestinal transport, the remaining unchanged drug is distributed in a steadily increasing volume of intestinal contents; the amount of drug immediately available for absorption per unit area of absorbing surface is decreased while the total area of contact between the absorbing gut wall and the drug-containing chymus is increased. If the drug were not distributed in a solid column but in an infinitely thin layer covering the gut wall, these effects would cancel out so that absorption would proceed as a first-order process independent of the area of intestinal surface actually participating in drug absorption. Even if the assumption of an infinitely thin layer is not valid, a first-order process frequently approximates the time course of absorption if absorption is fast.

In Kübler's equations (1–3), the length of the drug-containing chymus column and its transport rate are implicit parameters. They contribute significantly to the complexity without, however, giving much additional information since their influence on plasma concentrations is significant only during the relatively short intervals of entry and exit. These problems do not exist if absorption is treated as if it occurred from a small volume of chymus traveling down the intestinal tract at an arbitrary and even variable rate. This condition is true if a rapidly absorbed drug is released in a first-order process from a nondisintegrating preparation and may be a reasonable approximation in other cases.

PROCEDURE[1]

Consider a drug-containing volume of chymus that is so small that it passes through the absorbing length of intestine in a time interval shorter than the reciprocal of the corresponding sampling frequencies. With the assumption that absorption can be approximated reasonably well by a first-order process as discussed earlier, three equations are sufficient to describe the time course of plasma concentrations in a one-compartment open body model.

Let t_1 and t_2 be the points in time at which the drug enters and leaves the absorbing segment of intestine and let k_a and k_e be the apparent rate constants of absorption and elimination, respectively. Then, for $t < t_1$:

$$b = 0 \quad \text{(Eq. 5)}$$

For $t_1 < t < t_2$:

$$b = \frac{f D_0 k_a}{V_c (k_e - k_a)} [e^{-k_a(t - t_1)} - e^{-k_e(t - t_1)}] \quad \text{(Eq. 6)}$$

And for $t > t_2$:

$$b = \frac{f D_0 k_a}{V_c (k_e - k_a)} [e^{-k_a(t_2 - t_1)} - e^{-k_e(t_2 - t_1)}] e^{-k_e(t - t_2)} \quad \text{(Eq. 7)}$$

[1] Fitting programs are written in FORTRAN IV and were run on a PDP 11/10 computer with 24 K memory and RK 11/05 disk drive. They are available upon request to the author as listings and/or on cassettes.

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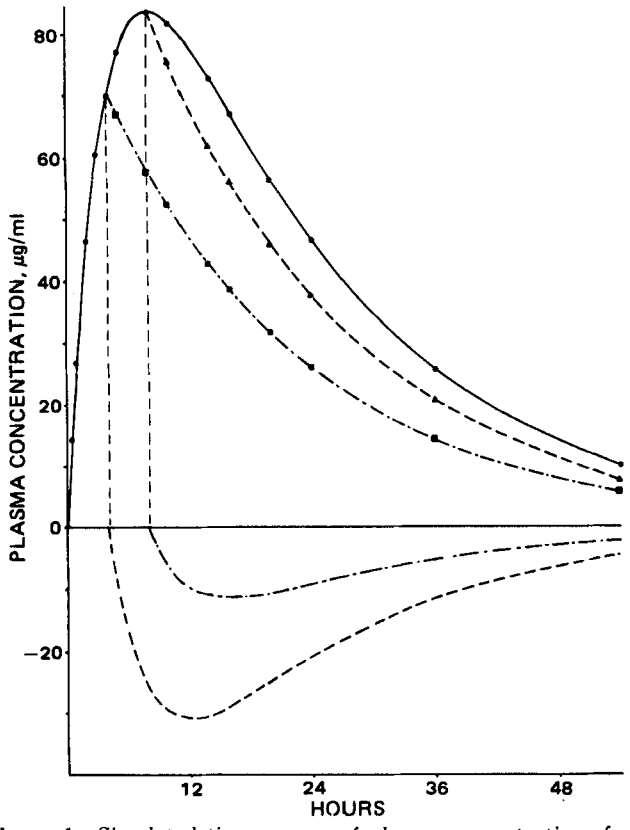

Figure 1—*Simulated time courses of plasma concentrations for a one-compartment model with truncated first-order absorption:*

Equation 18 Parameter Values	——	– – –	–·–·
k_e, hr^{-1}	*0.4*	*0.4*	*0.4*
k_e, hr^{-1}	*0.05*	*0.05*	*0.05*
V_c, *ml*	*8000.0*	*8000.0*	*8000.0*
f	*1*	*1*	*1*
t_1, *hr*	*0*	*0*	*0*
t_2, *hr*	*48.0*	*8.0*	*4.0*
D_0, *g*	*1.0*	*1.0*	*1.0*

There is a simpler and more generally applicable way to look at the problem. At $t = t_2$, the amount of drug not yet absorbed is:

$$D_1 = D_0 e^{-k_a(t_2-t_1)} \qquad \text{(Eq. 8)}$$

At all times $t > t_2$, plasma concentrations are lower by:

$$\Delta b = \frac{fD_0 e^{-k_a(t_2-t_1)}k_a}{V_c(k_e-k_a)}\left[e^{-k_a(t-t_2)} - e^{-k_e(t-t_2)}\right] \qquad \text{(Eq. 9)}$$

if absorption stops at $t = t_2$ than if absorption continues. This situation is illustrated in Fig. 1.

By extending the range of definition, Eqs. 5 and 6 can be combined to:

$$b = \frac{fD_0}{V_c}\zeta_0\frac{k_a}{(k_e-k_a)}\left[e^{-k_a(t-t_1)} - e^{-k_e(t-t_1)}\right] \qquad \text{(Eq. 10)}$$

where ζ_0 is:

$$\zeta_0 = \begin{cases} 0 & t < t_1 \\ 1 & t > t_1 \end{cases} \qquad \text{(Eq. 11)}$$

Similarly, an alternative to Eq. 9 is:

$$\Delta b = \frac{fD_0}{V_c}\zeta_1\frac{k_a}{(k_e-k_a)}\left[e^{-k_a(t-t_2)} - e^{-k_e(t-t_2)}\right] \qquad \text{(Eq. 12)}$$

with:

$$\zeta_1 = \begin{cases} 0 & t < t_2 \\ e^{-k_a(t_2-t_1)} & t > t_2 \end{cases} \qquad \text{(Eq. 13)}$$

According to the theorem, if $\mathcal{L}[F(t)] = f(s)$ and:

$$G(t) = \begin{cases} 0 & t < a \\ F(t-a) & t > a \end{cases} \qquad \text{(Eq. 14)}$$

then $\mathcal{L}[G(t)] = f(s)e^{-as}$, and one has the transforms:

$$\bar{b}(s) = \left(\frac{fD_0}{V_c}\right)(e^{-st_1})\left[\frac{k_a}{(k_e-k_a)(s+k_a)} + \frac{k_a}{(k_a-k_e)(s+k_e)}\right]$$
$$= \left(\frac{fD_0}{V_c}\right)(e^{-st_1})\left[\frac{k_a}{(s+k_a)(s+k_e)}\right] \qquad \text{(Eq. 15)}$$

and:

$$\bar{\Delta b}(s) = \left(\frac{fD_0}{V_c}\right)[e^{-k_a(t_2-t_1)}](e^{-st_2})\left[\frac{k_a}{(k_e-k_a)(s+k_a)} + \frac{k_a}{(k_a-k_e)(s+k_e)}\right]$$
$$= \left(\frac{fD_0}{V_c}\right)[e^{-k_a(t_2-t_1)}](e^{-st_2})\left[\frac{k_a}{(s+k_a)(s+k_e)}\right] \qquad \text{(Eq. 16)}$$

Subtracting Eq. 16 from Eq. 15 gives the transform of the function for concentrations in the body for a one-compartment model with first-order absorption starting at $t = t_1$ and stopping at $t = t_2$:

$$b(s) = \bar{b}(s) - \bar{\Delta b}(s) = \left(\frac{fD_0}{V_c}e^{-st_1}\right)\left[\frac{k_a}{(s+k_a)(s+k_e)}\right] - \left[\frac{fD_0}{V_c}e^{-k_a(t_2-t_1)}\right](e^{-st_2})\left[\frac{k_a}{(s+k_a)(s+k_e)}\right]$$
$$= \left(\frac{fD_0}{V_c}\right)\left[\frac{k_a}{(s+k_a)(s+k_e)}\right]\{e^{-st_1} - [e^{-k_a(t_2-t_1)}(e^{-st_2})]\} \qquad \text{(Eq. 17)}$$

This equation can be transformed back into the time domain:

$$b(t) = \frac{fD_0k_a}{V_c(k_e-k_a)}\{\zeta_0[e^{-k_a(t-t_1)} - e^{-k_e(t-t_1)}] - \zeta_1[e^{-k_a(t-t_2)} - e^{-k_e(t-t_2)}]\} \qquad \text{(Eq. 18)}$$

Thus, the input function for unlimited first-order absorption starting at zero time:

$$\text{in}_s = \frac{fD_0k_a}{(s+k_a)} \qquad \text{(Eq. 19)}$$

is replaced by:

$$\text{in}_s = \frac{fD_0k_a}{(s+k_a)}\{e^{-st_1} - [e^{-k_a(t_2-t_1)}(e^{-st_2})]\} \qquad \text{(Eq. 20)}$$

if the absorption rate is proportional to the amount of drug not yet absorbed during the time interval $t_1 < t < t_2$ but is zero otherwise.

A general equation for disposition from the central compartment of a linear mammillary model with n driving force compartments, where elimination may occur from any compartment, was given by Benet (4). Division by the volume of the central compartment changes the reference to concentrations rather than amounts:

$$d_{s,1} = \frac{1}{V_c}\frac{\prod_{i=2}^{n}(s+E_i)}{\prod_{i=1}^{n}(s+E_i) - \sum_{j=2}^{n}k_{1j}k_{j1}\prod_{\substack{m=2\\m\neq j}}^{n}(s+E_m)} = \frac{P(s)}{Q(s)} \qquad \text{(Eq. 21)}$$

where k_{1j} and k_{j1} are first-order rate constants for transfer from the central to the jth compartment and back, E_i is the sum of the exit rate constants from the ith compartment, and n is the number of driving force compartments. Both $P(s)$ and $Q(s)$ are polynomials in s, with Q being of higher degree than P so that partial fraction expansion is possible.

Alternatively, $Q(s)$ may be written as the product of its roots:

$$d_{s,1} = \frac{1}{V_c}\frac{P(s)}{\prod_{i=1}^{n}(s+\lambda_i)} \qquad \text{(Eq. 22)}$$

The convolution of the input function (Eq. 20) and the general disposition function (Eq. 22) is obtained by inverse transformation of their product formed in the Laplace domain:

$$c_{s,1} = \frac{fD_0}{V_c}\left[\frac{k_aP(s)}{\prod_{i=1}^{n}(s+\lambda_i)(s+k_a)}\right]\{e^{-st_1} - [e^{-k_a(t_2-t_1)}(e^{-st_2})]\} \qquad \text{(Eq. 23)}$$

Partial fraction expansion of the expression in the left brackets and introduction of shift-and-scale factors from the right brackets give, in the

time domain:

$$b(t) = \mathcal{L}^{-1}\{c_{s.1}\} = \frac{fD_0}{V_c}\left\{\zeta_0\left[\sum_{i=1}^{n} C_i e^{-\lambda_i(t-t_1)} + C_{n+1}e^{-k_a(t-t_1)}\right] - \zeta_1\left[\sum_{i=1}^{n} C_i e^{-\lambda_i(t-t_2)} + C_{n+1}e^{-k_a(t-t_2)}\right]\right\} \quad \text{(Eq. 24)}$$

Absorption from Several Segments—Where absorption does not drop to zero at t_2 but assumes a different finite value, there are two sequential absorption processes with first-order rate constants k_{a1} and k_{a2}. Although such a change may be due to transition into an intestinal segment with different absorption efficiency, alternative explanations can be a change in the release characteristics of the formulation or a change in the concentration of the absorbable drug species at the membrane caused by pH variations.

In this case, the situation is handled adequately by recursive application of Eq. 24 since all functions are linear and, therefore, additive. The system behaves as if absorption stopped completely at $t = t_2$ and as if a second dose of $D_0e^{-k_{a1}(t_1-t_2)}$ started to be absorbed simultaneously with a different rate constant k_{a2}. If absorption from the second segment approaches completion, the end of absorption due to drug removal from absorptive sites cannot be observed and just one more term is added to Eq. 24:

$$b(t) = \frac{fD_0}{V_c}\left\{\zeta_0\left[\sum_{i=1}^{n} C_{1i}e^{-\lambda_i(t-t_1)} + C_{1(n+1)}e^{-k_{a1}(t-t_1)}\right] - \zeta_1\left[\sum_{i=1}^{n} C_{1i}e^{-\lambda_i(t-t_2)} + C_{1(n+1)}e^{-k_{a1}(t-t_2)}\right] + \zeta_2\left[\sum_{i=1}^{n} C_{2i}e^{-\lambda_i(t-t_2)} + C_{2(n+1)}e^{-k_{a2}(t-t_2)}\right]\right\} \quad \text{(Eq. 25)}$$

which is readily extended to absorption from m segments in an n-compartment mammillary model, extending the definition given in Eq. 13:

$$\zeta_m = \begin{cases} 0 & t < t_{m+1} \\ \prod_{j=1}^{m} e^{-k_{aj}(t_{j+1}-t_j)} & t > t_{m+1} \end{cases} \quad \text{(Eq. 26)}$$

where k_{aj} is the absorption rate in the jth segment. In this notation, lag times are represented by an initial segment with index zero and absorption rate constant k_{a0} equal to zero. The generalized equation for this type of model is then:

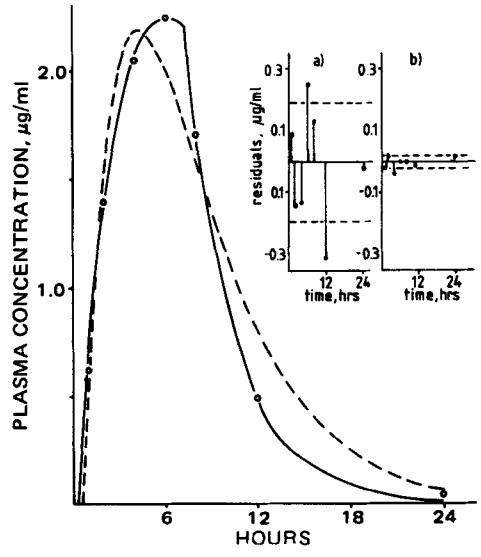

Figure 2—*Plasma griseofulvin concentrations in rats (5):*

Equation 18 Parameter Values	———	- - -
k_a, hr^{-1}	*0.09066*	*0.2602*
k_e, hr^{-1}	*0.3090*	*0.2944*
V_c/f, *ml/k*	*3939.3*	*7952.0*
t_1, *hr*	*0.3612*	*0.6387*
t_2, *hr*	*7.168*	*>24.0*
D_0, *mg/k*	*50.0*	*50.0*

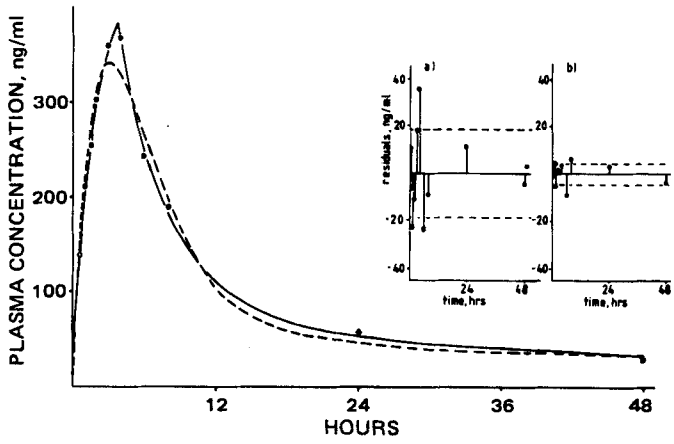

Figure 3—*Plasma buformin levels in humans (sustained-released preparation) (7):*

$$C_1 = \frac{k_a(k_{21}-\alpha)}{(k_a-\alpha)(\beta-\alpha)} \quad C_2 = \frac{k_a(k_{21}-\beta)}{(k_a-\beta)(\alpha-\beta)} \quad C_3 = \frac{k_a(k_{21}-k_a)}{(\alpha-k_a)(\beta-k_a)}$$

$$\lambda_1 = \alpha \qquad \lambda_2 = \beta$$

Equation 24 Parameter Values	———	- - -
k_a, hr^{-1}	*0.1836*	*0.3422*
k_{21}, hr^{-1}	*0.05106*	*0.03523*
α, hr^{-1}	*0.2362*	*0.3420*
β, hr^{-1}	*0.0202*	*0.01314*
t_1, *hr*	*−0.3016*	*0.0*
t_2, *hr*	*3.722*	*>60.0*
V_c/f, *liters*	*3203.4*	*90.04*
D_0, *mg*	*100*	*100*

$$b(t) = \frac{fD_0}{V_c}\left\{\sum_{j=1}^{m}\left[\zeta_{j-1}\left(\sum_{i=1}^{n} C_{ji}e^{-\lambda_i(t-t_j)} + C_{(j)(n+1)}e^{-k_{aj}(t-t_j)}\right) - \zeta_j\left(\sum_{i=1}^{n} C_{ji}e^{-\lambda_i(t-t_{j+1})} + C_{(j)(n+1)}e^{-k_{aj}(t-t_{j+1})}\right)\right]\right\} \quad \text{(Eq. 27)}$$

Each segment is thus represented by two terms, both zero before the segment becomes involved in absorption. At this time, the first term assumes positive values whereas the second term changes to smaller negative values as soon as the segment is no longer active in absorption.

The solution is very general and of little use in any practical situation. Nevertheless, it indicates that any time course of absorption, however irregular, can be approximated by a sequence of first-order absorption processes, provided that the set of measurements is accurate and large enough. In fact the same effect can be achieved by a sequence of any well-defined input processes. An example is the simulation of first-order absorption by a sequence of zero-order infusions with decreasing rates, which Loo and Riegelman (5) used to demonstrate the applicability of their method of calculating intrinsic absorption rates. In this context, repeated administration of identical doses at equal time intervals may be viewed as an imperfect realization of a zero-order input function; the approximation becomes more and more perfect as the time intervals between administrations decrease.

Zero-Order Absorption—Since the liberation of rapidly absorbed drugs from sustained-release preparations ideally should be close to a zero-order process, this case will be touched on briefly. With ζ_1 and ζ_2 defined as:

$$\zeta_1 = \begin{cases} 0 & t < t_1 \\ 1 & t > t_1 \end{cases} \quad \text{(Eq. 28a)}$$

$$\zeta_2 = \begin{cases} 0 & t < t_2 \\ 1 & t > t_2 \end{cases} \quad \text{(Eq. 28b)}$$

the time course of plasma concentrations during and after zero-order infusion of a drug, conferring the properties of a two-compartment model upon the body, is given by:

$$b(t) = \frac{k_0}{V_c}\left\{\zeta_1\left[\frac{k_{21}}{\alpha\beta} + \frac{k_{21}-\alpha}{\alpha(\alpha-\beta)}e^{-\alpha(t-t_1)} + \frac{\beta-k_{21}}{\beta(\alpha-\beta)}e^{-\beta(t-t_1)}\right] - \zeta_2\left[\frac{k_{21}}{\alpha\beta} + \frac{k_{21}-\alpha}{\alpha(\alpha-\beta)}e^{-\alpha(t-t_2)} + \frac{\beta-k_{21}}{\beta(\alpha-\beta)}e^{-\beta(t-t_2)}\right]\right\} \quad \text{(Eq. 29)}$$

and, after rearrangement:

$$b(t) = \frac{k_0}{V_c}\left\{\frac{k_{21}}{\alpha\beta}(\zeta_1 - \zeta_2) + \frac{k_{21} - \alpha}{\alpha(\alpha - \beta)}[\zeta_1 e^{-\alpha(t-t_1)} - \zeta_2 e^{-\alpha(t-t_2)}] + \frac{\beta - k_{21}}{\beta(\alpha - \beta)}[\zeta_1 e^{-\beta(t-t_1)} - \zeta_2 e^{-\beta(t-t_2)}]\right\} \quad \text{(Eq. 30)}$$

where t_1 is the time when infusion starts and t_2 is the time when it stops.

The zero-order rate constant can be expressed as $k_0 = [D_0/(t_2 - t_1)]$.

In zero-order intestinal absorption, t_1 is the time of onset of release and t_2 is the time when the formulation is exhausted. Linear losses by gut wall metabolism and nonsaturable first-pass metabolism may be considered by multiplying Eq. 29 by a factor, f, which is smaller than or equal to unity. In this case, f is not a quotient of the rate constants but still reflects the fraction of absorbed drug that reaches the general circulation.

Let t_3 be the time when the formulation leaves the absorbing segment of the intestine, which may be earlier or later than t_2. For $t_2 < t_3$:

$$b = \frac{fD_0}{V_c(t_2 - t_1)}\left\{\frac{k_{21}}{\alpha\beta}(\zeta_1 - \zeta_2) + \frac{k_{21} - \alpha}{\alpha(\alpha - \beta)}[\zeta_1 e^{-\alpha(t-t_1)} - \zeta_2 e^{-\alpha(t-t_2)}] + \frac{\beta - k_{21}}{\beta(\alpha - \beta)}[\zeta_1 e^{-\beta(t-t_1)} - \zeta_2 e^{-\beta(t-t_2)}]\right\} \quad \text{(Eq. 31)}$$

For $t_2 > t_3$:

$$b = \frac{fD_0}{V_c(t_2 - t_1)}\left\{\frac{k_{21}}{\alpha\beta}(\zeta_1 - \zeta_3) + \frac{k_{21} - \alpha}{\alpha(\alpha - \beta)}[\zeta_1 e^{-\alpha(t-t_1)} - \zeta_3 e^{-\alpha(t-t_3)}] + \frac{\beta - k_{21}}{\beta(\alpha - \beta)}[\zeta_1 e^{-\beta(t-t_1)} - \zeta_3 e^{-\beta(t-t_3)}]\right\} \quad \text{(Eq. 32)}$$

where:

$$\zeta_3 = \begin{cases} 0 & t < t_3 \\ 1 & t > t_3 \end{cases} \quad \text{(Eq. 33)}$$

The difference between this case and an intravenous infusion is that complete bioavailability is no longer assured and that the input rate and duration are no longer experimental variables with known values but are model parameters to which values have to be assigned.

Examples—Three examples from the literature (6–9) are given in which time-limited absorption explained experimental data better than models with continuing absorption. In the papers quoted, observations on individuals are reported. Time courses of the best-fitting continuous absorption models are indicated by broken lines; corresponding functions with truncated absorption are solid.

Griseofulvin—Carrigan and Bates (6) administered doses of 50 mg of micronized griseofulvin/kg to rats. The drug was given in an aqueous suspension, in a corn oil suspension, and in a triphasic system with griseofulvin suspended in a corn oil-in-water emulsion. Polysorbate 60

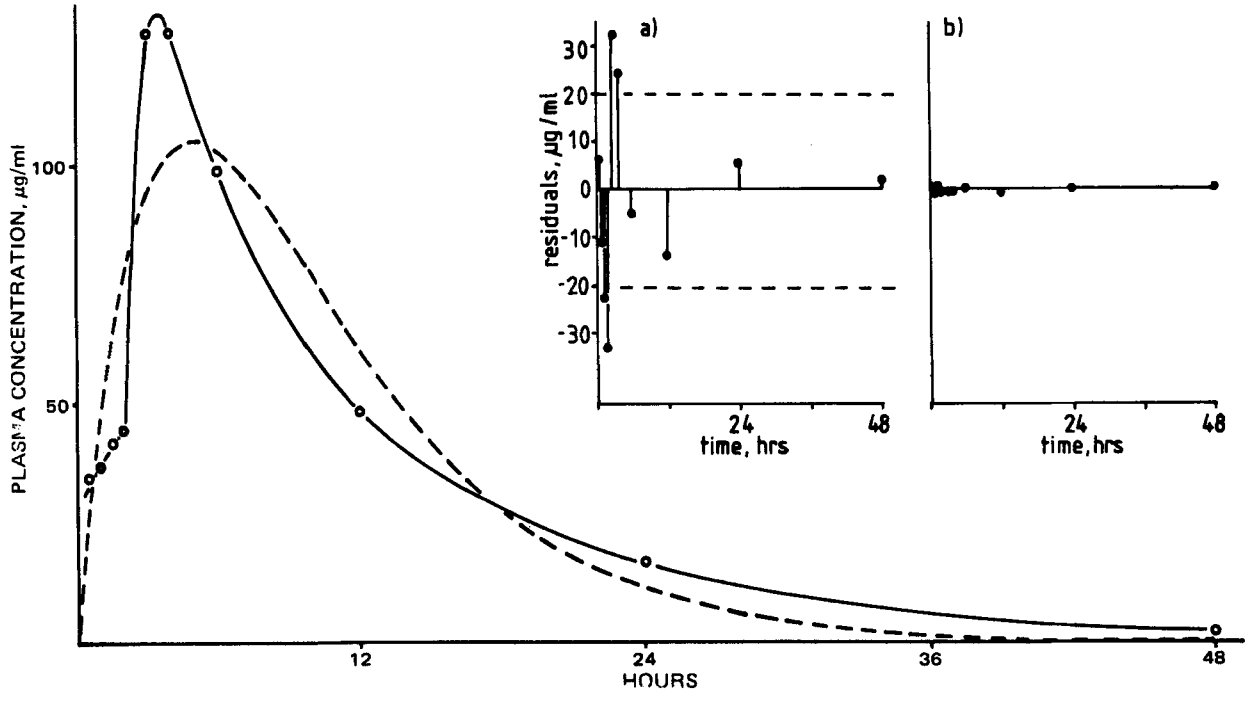

Figure 4—*Plasma sulfisoxazole concentrations in humans after oral administration (8):*

$$C_{11} = \frac{k_{a1}(k_{21} - \alpha)}{(k_{a1} - \alpha)(\beta - \alpha)} \quad C_{12} = \frac{k_{a1}(k_{21} - \beta)}{(k_{a1} - \beta)(\alpha - \beta)} \quad C_{13} = \frac{k_{a1}(k_{21} - k_{a1})}{(\alpha - k_{a1})(\beta - k_{a1})}$$

$$C_{21} = \frac{k_{a2}(k_{21} - \alpha)}{(k_{a2} - \alpha)(\beta - \alpha)} \quad C_{22} = \frac{k_{a2}(k_{21} - \beta)}{(k_{a2} - \beta)(\alpha - \beta)} \quad C_{23} = \frac{k_{a2}(k_{21} - k_{a2})}{(\alpha - k_{a2})(\beta - k_{a2})}$$

$$\lambda_1 = \alpha \quad \lambda_2 = \beta \quad \zeta_0 = \begin{cases} 0 & t < t_1 \\ 1 & t > t_1 \end{cases} \quad \zeta_1 = \begin{cases} 0 & t < t_2 \\ e^{-k_{a1}(t_2 - t_1)} & t > t_2 \end{cases}$$

Equation 27 Parameter Values	
k_{a1}, hr^{-1}	*0.1080*
k_{a2}, hr^{-1}	*1.6788*
k_{21}, hr^{-1}	*0.1941*
α, hr^{-1}	*0.2938*
β, hr^{-1}	*0.08086*
t_1, *hr*	*−1.6656*
t_2, *hr*	*2.0807*
V_c, *ml*	*10749.0*
fD_0, *g*	*2.0*

Equation 6 Parameter Values	
k_a, hr^{-1}	*0.2013*
k_e, hr^{-1}	*0.2010*
V_c/f, *ml*	*6978.0*
t_1, *hr*	*0.0*
t_2, *hr*	*>48.0*
D_0, *g*	*2.0*

was added to all preparations. Seven samples were obtained between 1 and 24 hr after administration. Significant differences in peak plasma levels attributable to the liquid phases were observed with mean values of 0.892, 1.30, and 2.07 μg/ml, respectively. There were no corresponding shifts in the times when peak concentrations occurred.

Figure 2 shows data from an animal that received the drug suspended in corn oil. The peak plasma level was the highest in its group and occurred late. The better fit of the discontinuous model, although conspicuous, is statistically not significant because of the small number of degrees of freedom for the truncated absorption model (five parameters are estimated from seven observations).

Buformin—A two-compartment model is adequate to describe the plasma concentration–time course after injection of buformin (7). The drug is not metabolized. A sustained-release formulation containing 100 mg of ^{14}C-buformin hydrochloride in a wax matrix was administered to six diabetic patients (8). Ten plasma samples were taken during 48 hr after ingestion. Both urinary and fecal excretion were followed.

Figure 3 gives the plasma data for one subject. As predicted on the basis of *in vitro* liberation studies, release and absorption appear to be first order, although truncated. (Zero order was tested and gave a reasonable but inferior fit.) Fecal recovery was 44.8% of the dose, and 38.4% was excreted during the first 24 hr by this route. This finding is consistent with a fecal excretion of 48% predicted by the truncated absorption model. The negative lag time obtained in the fit is indicative of a short phase of rapid absorption, which cannot be resolved on the basis of the sampling schedule used. The variances of the residuals are 355.8 and 20.09 $(ng/ml)^2$ for the continuous and truncated absorption models with five and three degrees of freedom. Therefore, the latter model is significantly better on the 95% confidence level.

Sulfisoxazole—Kaplan *et al.* (9) compared sulfisoxazole pharmacokinetic profiles after intravenous, intramuscular, and oral administrations to six volunteers. After intravenous injection, the plasma concentration–time course corresponded to a two-compartment model. The data given in Fig. 4 were observed in the third subject after oral administration of a 2.0-g dose. It stands out among the experiments reported in this paper because of its apparent absence of scatter. Although a two-compartment, two-segment absorption model gives an excellent fit, there remains some doubt about its general applicability for the drug and the formulation used. Again, a negative lag time indicates that there is an initial phase of rapid absorption.

Attempts to fit these data by a two-compartment model with continuing first-order kinetics failed because the model degenerated when k_a, α, and β became identical within the first three significant digits. Therefore, a one-compartment model with unlimited absorption was used for comparison. With residual variances of 404.38 and 0.1337 $(\mu g/ml)^2$ for seven and two degrees of freedom, the biphasic absorption model is superior on the 99% confidence level.

DISCUSSION

The type of models presented is not really new except for the notation, which was in part adapted from electronics (10). Time-limited intestinal absorption was demonstrated for lincomycin and clindamycin (11) and applied to the rectal absorption of lincomycin and aspirin as well, where the fraction of dose absorbed increased with retention time (12, 13).

Hybrids of flow models for absorption and compartmental models for distribution, metabolism, and elimination have advantages over a purely compartmental approach, which is included as a limiting case. Even in the simplest single-segment version, they provide a logical link between the rate and amount aspects of bioavailability and eliminate the flip-flop phenomenon if absorption is incomplete. Multisegment models are flexible tools to obtain more information about the time course of absorption. The models are parsimonious since a minimum of new parameters (one rate constant and an exit time) is introduced for each absorption segment and good exit time estimates can be found by simple inspection of the data. They appear to be superior over models approximating the intestine by a chain of compartments, as recently proposed by Hradil *et al.* (14), since they avoid the physiologically doubtful assumption of first-order transport between gut sections, which gives rise to poorly defined transition rate constants.

If absorption stops abruptly, the graphical method of residuals fails as shown in Fig. 5, in which simulated data from Fig. 1 were redrawn semilogarithmically. As discussed by Perrier and Gibaldi (15), apparent absorption rates increase when only the absorption time interval is shortened. Other procedures to set up fraction absorbed *versus* time plots (5, 16) are still operative, but, like all sequential data analysis methods,

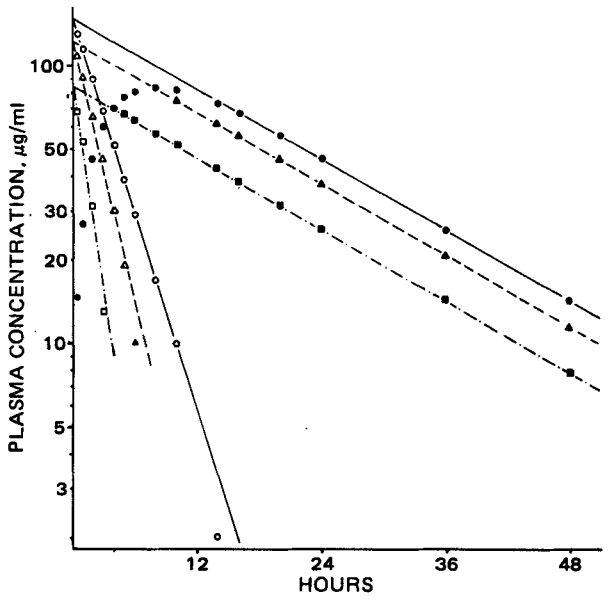

Figure 5—*Failure of the method of residuals if applied to data from Fig. 1.*

they suffer from error propagation problems and are ineffective if few samples are taken during the absorption phase.

Some problems are associated with the type of models proposed here. Obviously, spline functions cannot be used for interpolation in the neighborhood of discontinuities. Less obviously, commonly used fitting algorithms, such as the Gauss–Newton method, require that derivatives of model equations with respect to their parameters are continuous. This condition is not true for transition times and reduces both the computation efficiency and the precision of the final estimates. This problem does not occur if inherently less efficient direct search strategies, such as the Nelder–Mead method (17), are applied.

The increase in adaptability to measurements makes truncated absorption models more vulnerable to influences of experimental error than more rigid alternatives, and the ease of improving a fit by just throwing in another absorption segment adds to this problem. The risk can be controlled by careful analysis of the residuals and, possibly, by inspection of confidence contours of the parameter estimates. In test calculations, a typical error, indicating improper use of limited absorption models, was a significant underestimation of the central compartment volume.

Time-limited absorption models are implemented easily on both analog and digital computers and can be valuable tools in further studies of intestinal drug absorption. They can also provide diagnostic help if absorption kinetics are pathologically altered, as in mucoviscidosis[2].

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NMR Spectroscopic Determination of Preferred Conformations of Quinidine and Hydroquinidine

YEHUDA YANUKA, SHIMONA YOSSELSON SUPERSTINE, and EDWARD SUPERSTINE ˣ

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Abstract □ NMR spectra of quinidine (I), hydroquinidine (II), and their respective acetyl derivatives (III and IV) were compared. The chemical shifts of some protons in I differed from those of their counterparts in II. These values were concentration dependent in I and II; they were similar in III and IV but not concentration dependent. The implications of these findings and the correlation of the NMR data with the preferred conformations are discussed.

Keyphrases □ Quinidine—conformation, NMR spectroscopic analysis, concentration dependence □ Hydroquinidine—conformation, NMR spectroscopic analysis, concentration dependence □ NMR spectroscopy—quinidine and hydroquinidine, conformations, concentration dependence

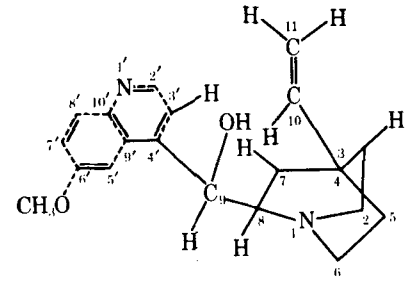
Of all of the cinchona alkaloids, quinidine (I) remains the most important because of its extensive use as an antiarrhythmic agent. Hydroquinidine (II) is an impurity found in commercial I and also has antiarrhythmic activity. The absolute configuration of all asymmetric carbon atoms in these molecules has been assigned by different methods including NMR spectroscopy (1–4). The evidence of these studies is considered conclusive.

No comprehensive studies have been carried out concerning the conformation of the different fragments of I and II. Knowledge concerning the preferred stable conformation of these compounds facilitates structural elucidation of the metabolic products. The objectives of this work were to analyze the NMR spectra of I and II and their 9-acetyl derivatives III and IV, stressing the importance of acetylation, and to discover new information related to their structure and conformation.

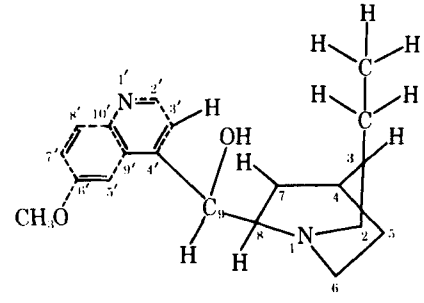
EXPERIMENTAL

Spectra were obtained at 100 MHz using an analytical NMR spectrometer[1] equipped with an automatic recorder. Tetramethylsilane in deuterochloroform was used as the internal standard; the chemical shift of its protons does not appear in the spectra. Pure I and II were obtained from commercial quinidine sulfate[2]. TLC and preparative TLC were carried out on aluminum oxide[3] plates. The developing solvent was ethyl acetate.

Purification of Commercial Quinidine—Commercial quinidine sulfate (500 mg) was dissolved in water (20 ml). A slight excess of sodium bicarbonate was added, and the free base was extracted in a separator by three 30-ml portions of chloroform. The chloroform solution was filtered through anhydrous sodium sulfate and evaporated.



I



II

Portions of the free base (30 mg) were chromatographed on aluminum oxide plates. The fluorescing material was viewed under UV light and divided into three fractions. The upper strip was scraped and dispersed in 20 ml of 0.1 *N* H_2SO_4. Sodium bicarbonate (240 mg) was added, and pure quinidine was extracted with chloroform. The mixture was transferred to a separator, and the chloroform solution was filtered through anhydrous sodium sulfate and evaporated. A readily crystallized pure quinidine was obtained after solvent removal, mp 170–171°, R_f 0.135 (chloroform–ethyl acetate, 2:1). The NMR spectrum is shown in Fig. 1.

The lower strip, containing II contaminated by small quantities of I, was scraped and extracted as described. Pure II was obtained by a repetition of the chromatographic procedure. Recrystallization from methanol yielded crystals, mp 169° [lit. (5) mp 169 and 174°]; R_f 0.1 (chloroform–ethyl acetate, 2:1). The NMR spectral data are given in Table I.

Acetylation—Pure quinidine (40 mg) was dissolved in pyridine (1 ml), and acetic anhydride (1 ml) was added. The reaction mixture was allowed to stand at room temperature for 24 hr. Solvents were removed with an air stream, and the solid residue was dissolved in 30 ml of chloroform. The

[1] Varian A-100 D.
[2] Quinidine sulfate USP, Sigma Chemical Co., St. Louis, Mo.
[3] Aluminum oxide GF 254, Stahl, Merck.

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