Interpretation of Plasma Concentration–Time Curves after Oral Dosing

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Abstract □ The pharmacokinetic information obtained after oral administration is examined using the two-compartment model. Data were obtained by simulation and experimentally by administering sulfisoxazole by an exponential infusion to rabbits. When the absorption rate constant is allowed to approach α, a typical two-compartment oral absorption curve is obtained, which is described by a triexponential equation. However, if the absorption rate constant approaches E_2 (the sum of the elimination rate constants out of the peripheral compartment), the data are adequately fit by a one-compartment model, with the calculated absorption rate equal to α. The relative error in using a one-compartment model to calculate absorption rate constants for two-compartment data is also evaluated.

Keyphrases □ Pharmacokinetics—interpretation of plasma concentration–time curves after oral administration of sulfisoxazole, rabbits □ Absorption rate constants—data fitted to one- and two-compartment models, relative error evaluated, oral administration of sulfisoxazole, rabbits □ Oral administration—sulfisoxazole, interpretation of plasma concentration–time curves, rabbits □ Sulfisoxazole—oral administration, interpretation of plasma concentration–time curves, rabbits □ Antibacterial agents—sulfisoxazole, oral administration, interpretation of plasma concentration–time curves, rabbits

One major problem confronting the drug industry is the correlation of *in vitro* dissolution studies with *in vivo* absorption measurements for oral dosage forms. Information can be gained about the pharmacokinetics of a drug and the relative efficacy of its oral dosage forms from oral plasma concentration–time curves where no data exist describing the drug disposition after intravenous administration. Although it would always be better to have intravenous data in humans, regulations and therapeutic considerations often dictate situations where this kind of data is not available even for drugs in current clinical use. The present work describes a situation where completely invalid measurements of absorption rates would be obtained if previous intravenous measurements had not been made.

The determination of absorption rate constants that depend on the model used to describe the disposition kinetics of the drug after an intravenous dose has been the subject of several publications. Most absorption calculations have been made using a one- or two-compartment body model. The Wagner–Nelson method (1) has been used for drugs seemingly described by the one-compartment model, and the Loo–Riegelman method (2) has been used for those following kinetics consistent with the two-compartment model. The representative equations for the one- (Eq. 1) and two-compartment (Eq. 2) models are:

$$C_p = \frac{k_{a1}FD}{V_d(k_{a1} - k_d)}(e^{-k_d t} - e^{-k_{a1}t}) \qquad \text{(Eq. 1)}$$

and:

$$C_p = \frac{k_{a2}FD}{V_1}\left[\frac{(E_2 - k_{a2})}{(\alpha - k_{a2})(\beta - k_{a2})}e^{-k_{a2}t} + \frac{(E_2 - \alpha)}{(\beta - \alpha)(k_{a2} - \alpha)}e^{-\alpha t} + \frac{(E_2 - \beta)}{(\alpha - \beta)(k_{a2} - \beta)}e^{-\beta t}\right] \qquad \text{(Eq. 2)}$$

where:

C_p = plasma concentration
FD = available dose
k_{a1} = absorption rate constant, one-compartment body model
k_{a2} = absorption rate constant, two-compartment body model
k_d = elimination rate constant, one-compartment body model
E_2 = sum of the exit (or micro) rate constants out of Compartment 2 in a two-compartment model
α, β = disposition (or macro) constants describing distribution and elimination in a two-compartment model
V_d, V_c = volumes of distribution for a one-compartment model and central compartment of a two-compartment model, respectively.

The term "flip-flop model" has been used recently to illustrate the nonuniqueness of any concentration–time curve believed to describe first-order input and disposition from a one-compartment pharmacokinetic model, since the slow rate constant may be attributed to *either* absorption or elimination and the fast rate constant may be attributed to the alternate. Therefore, it is impossible to tell from a single curve (following an oral dose) whether the terminal half-life is due to absorption or elimination. The two-compartment model is somewhat more unique in that it does take on characteristic shapes depending on the relative size of the absorption rate constant with respect to α, β, or E_2.

In this study, generated curves are used to illustrate characteristic shapes and to compare one- and two-compartment analyses. In addition, representative curves were obtained experimentally in the rabbit, using sulfisoxazole [N^1-(3,4-dimethyl-5-isoxazolyl)sulfanilamide]. Oral absorption was simulated experimentally with a logarithmic infusion.

EXPERIMENTAL

The left and right marginal ear veins of 4-kg rabbits were cannulated[1], one ear being used for chronic sampling and the other ear for drug administration. One-milliliter blood samples were taken at frequent intervals and analyzed according to the Bratton–Marshall method (3). Initially, the drug was administered as a bolus injection, and the disposition parameters were calculated from the plasma concentration–time curve.

Subsequent experiments were run in which oral absorption was simulated by administering the drug by a first-order intravenous infusion, accomplished by exponential dilution of a drug solution with the apparatus represented in Fig. 1. A 5–10-ml disposable syringe (pictured) on the left was fixed at a constant volume, while a 50-100-ml syringe in a Harvard syringe pump determined the flow and constantly diluted the

[1] Intracath catheter sets.

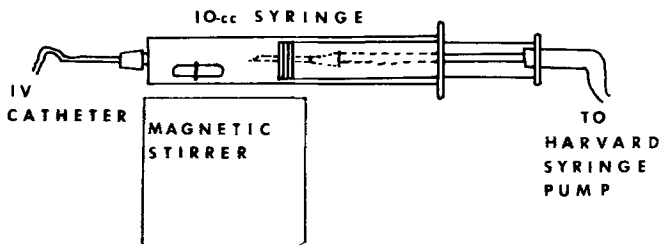

Figure 1—*Apparatus used to administer first-order infusions intravenously.*

contents in the small syringe with dextrose (5%). A magnetic stirring bar was activated in the small syringe to ensure proper mixing. Any first-order infusion rate can be obtained by proper selection of the infusion rate in milliliters per minute on the Harvard infusion pump and the appropriate fixed volume of the small syringe.

The value of the simulated first-order absorption rate constant is equal to the zero-order infusion rate (maintained with the infusion pump) divided by the fixed volume in the small syringe. Each infusion was continued until at least 97% of the dose was administered. Both the experimental sulfisoxazole data and the generated data were fit on a digital computer[2] using the nonlinear least-squares fitting program NONLIN (4).

RESULTS AND DISCUSSION

Analysis of oral data can be very inexact, since oral absorption often adds more than one variable to the intravenous data even though the data appear to be fit adequately by addition of a single exponential term and an availability constant. However, this "smoothed" interpretation of the absorption process may include variations due to nonlinearities in dosage form release and dissolution of the drug, first-pass effects and decreased physiological availability, stomach emptying, biliary recycling, blood flow to the GI tract, and other problems of non-first-order absorption related to distribution into and diffusion through the GI membrane. However, despite the complexity of the absorption process, there are numerous examples of oral absorption being adequately described by a single first-order process. This may be due to the lack of sufficient blood level data to model the absorption process precisely or to the fact that one of these processes becomes rate limiting, thereby simplifying the absorption mechanism into a process that may be described by a single exponential term.

A single first-order absorption process, commonly used in pharmacokinetic modeling, is assumed for the remainder of this discussion. If absorption can be represented by a first-order process, then, in the case of the two-compartment model, the shape of the blood level curve can

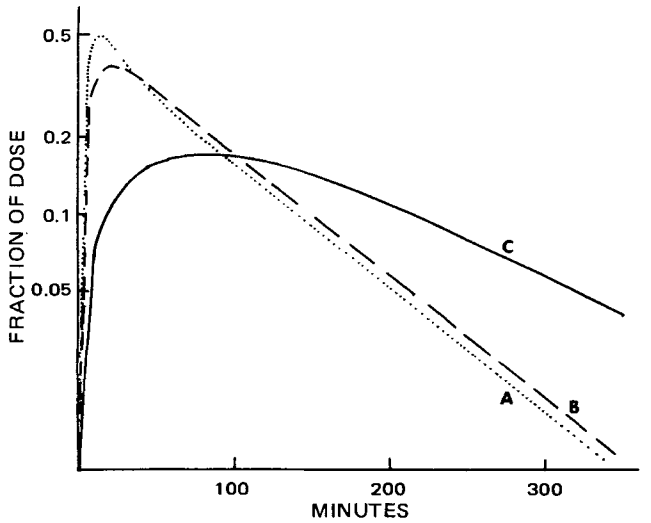

Figure 2—*Blood level curves for two-compartment model following first-order absorption. Key: A,* $k_{a2} \simeq \alpha$; *B,* $k_{a2} \simeq E_2$; *and C,* $k_{a2} \simeq \beta$.

[2] IBM 360/50.

Table I—Comparison of One-Compartment Analysis of Two-Compartment-Generated Data

Case	Two Compartment[a], k_{a2}, hr^{-1}	One Compartment	
		k_{a1}, hr^{-1}	k_d, hr^{-1}
A	7.2	25.9	0.83
D	5.4	14.1	0.76
B	3.6	7.54	0.67
E	1.8	2.58	0.61
C	0.6	1.10	0.40

[a] The two-compartment rate constants were $\alpha = 7.46\ hr^{-1}$, $\beta = 0.67\ hr^{-1}$, and $E_2 = 3.57\ hr^{-1}$.

be indicative of the relative size of the absorption rate constant. Figure 2 illustrates three blood level curves, generated using the same two-compartment rate constants (given in the left-hand side of Table I) and differing only in the absorption rate constants following oral dosing. Curve A is characterized by a "nose," which can be visualized by extrapolating back the log-linear line and having a convex curve lie above it. Curve A is generally thought to be characteristic of a two-compartment model, whereas curve B is often representative of a one-compartment model.

Curve A in Fig. 2 is an example of a case where the absorption rate constant approached α ($k_{a2} = 7.2$, $\alpha = 7.46$). When referring to Eq. 2, it is important to realize that although two of the exponentials are almost equal to each other, this triexponential equation does not simplify to a biexponential equation. This predominant nose is characteristic of a two-compartment model when k_{a2} is larger than E_2 and approaching or larger than α. However, based on oral data alone, it is not possible to predict whether the larger rate constant in the triexponential equation describing this curve should be assigned to k_{a2} or α.

Curve B of Fig. 2 illustrates a curve apparently following a one-compartment model. Actually, this curve was generated with the two-compartment equation and the rate constants given in the left-hand side of Table I, but with k_{a2} very nearly equal to E_2 ($k_{a2} = 3.6$, $E_2 = 3.57$). This curve could be perfectly fit to a one-compartment model. The slow rate constant could be correctly assigned to β. However, the fast rate constant, regardless of whether it was obtained by the method of residuals or by a computer fit, would not be equal to the absorption rate constant k_{a2} but rather equal to α. This result can be explained quite easily by referring to Eq. 2. As k_{a2} approaches E_2, the coefficient of the exponential term describing absorption approaches zero.

Curves A and B in Fig. 2 could present a perplexing problem if they resulted from the administration of two different dosage forms of the same drug. That is, both dosage forms seem to be equally available (from a comparison of areas under the curves) and to have the same slow rate of disposition from the body (both curves are parallel and log linear after 1 hr). However, dosage form B appears to follow a one-compartment body model and dosage form A follows a two-compartment body model. And, if each set of data is treated by the seemingly appropriate model, the absorption rates calculated would almost be equal.

Curve C in Fig. 2 is an example of a case where k_{a2} is allowed to approach β ($k_{a2} = 0.6$, $\beta = 0.67$). Here, it appears that the data could be fit by either a one- or two-compartment model, depending upon the number and preciseness of the data points. Even though this curve is described by a triexponential equation, it will not have the characteristic nose of curve A. If the oral blood curve is of this form, it is not possible to make a unique assignment of the slow rate constant to either β or k_{a2} when only a single oral data curve is available.

Even though the investigator may fit oral data to the seemingly appropriate model, significant errors may occur when interpreting and comparing the absorption rate constants. In cases such as these, inconsistencies between the relative absorption rate constants and relative times of peak concentration may arise. Time of peak concentration should be a reliable relative measurement since it is model independent. That is, from the peak times in Fig. 2, the investigator should know that the absorption rate constant for curve A is greater than that for curve B, which is greater than that for curve C. However, due to experimental error, it is often difficult to define the peak time precisely. In addition, any lag time greatly influences the peak time and may invalidate comparisons between different dosage forms based upon peak time measurements.

Similar data obtained experimentally for sulfisoxazole are pictured in Fig. 3. The parameters obtained after an intravenous dose (curve A)

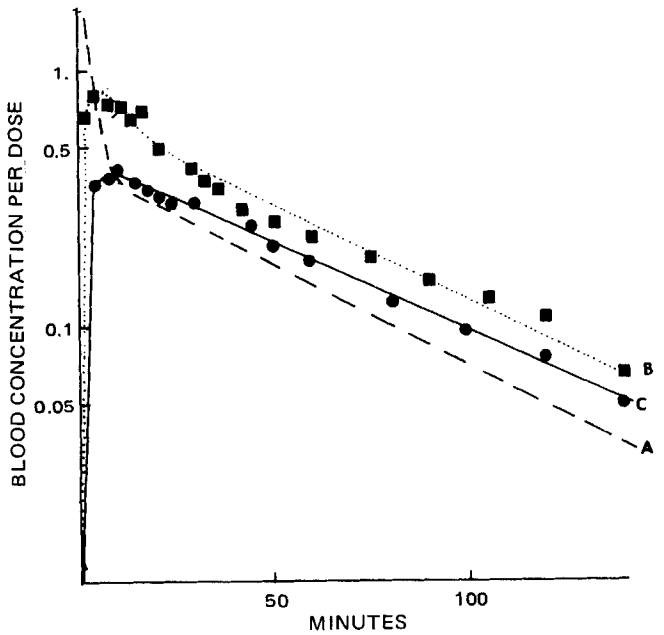

Figure 3—*Blood sulfisoxazole levels in the rabbit following intravenous administration as a bolus and as two different first-order infusions. Key: A, intravenous bolus; B,* $k_{a2} = 0.16$*; and C,* $k_{a2} = 0.08$.

were $\alpha = 0.45$, $\beta = 0.018$, and $E_2 = 0.11$. Curve B, the result of a first-order infusion (with a rate constant of 0.16), is obviously two-compartment data and was fit to Eq. 2. The computer-fitted parameters for curve B were equal to the intravenous disposition parameters and the actual absorption rate constant (0.16). Curve C appears to be one-compartment data and was fit to Eq. 1, resulting in fitted values of $k_{a1} = 0.47$ and $k_d = 0.016$. These values are approximately equal to the α and β obtained with the intravenous data. The actual k_a in this case was 0.08, a value less than E_2. Without the intravenous curve, there would be an apparent inconsistency to these data. Curve B has a characteristic nose, yielding an absorption rate constant of either 0.45 or 0.16 since the investigator cannot distinguish between k_{a2} and α. The apparent one-compartment data (curve C), in which absorption appears to be slightly slower on the basis of the peak time comparisons, yields an absorption rate constant of 0.47.

Wagner and Metzler (5) showed that simulated two-compartment blood level data can often be fit with minimal error to a one-compartment model. Table I gives the results from computer fitting the two-compartment data illustrated in Fig. 2 (A, B, and C) and two intermediate absorption rate constants (D and E) to a biexponential equation (Eq. 1). The best-fit absorption and elimination rate constants for the one-compartment model are listed. Although the computer-fitted absorption rate constants yield marked overestimates of the real absorption rate constants, the relative order of these fitted constants agrees with the relative order of the real absorption constants. In the case where k_{a2} approaches E_2, the computed absorption rate constant, k_{a1}, approaches α.

Wagner (6) suggested that even in cases where the one-compartment fit is poor, the ratio of the absorption rate constants calculated for two dosage forms using one-compartment analyses would be a good approximation of the actual ratio of the absorption rate constants. Such a comparison was made using the values in Table I. Table II gives the ratios of the fitted or determined absorption constants using a one-compartment model (k_{a1x}/k_{a1y}) in comparison to the ratio of the actual absorption constants (k_{a2x}/k_{a2y}), followed by a column giving the percent error found in the computer-fitted ratio with respect to the actual ratio. Although the percent error is quite large in some cases, an evaluation of the relative rank merits of different dosage forms can be accurately determined with one-compartment fits, as pointed out by Wagner (6).

SUMMARY

The present work analyzes the information that may be obtained concerning the pharmacokinetics of drug absorption from oral plasma concentration–time curves when no data exist describing drug disposition after intravenous administration. All examples used here describe the absorption process by a single rate constant, although this constant may represent the best fit to limited data for a very complex multistep process.

Sulfisoxazole, a drug following two-compartment kinetics after an intravenous bolus, is infused logarithmically into male rabbits at absorption rates approximately equal to values found for α, β, and E_2 (data determined from intravenous bolus data) in addition to rates between and above these values. When the absorption rate approaches α, the data points yield a curve consistent with the usual two-compartment oral absorption picture where a relatively fast absorption rate constant gives a large hump or nose in the early part of the curve. However, when the absorption rate is close to E_2, the data are best fit by a one-compartment model. Yet, the "absorption rate" calculated from these data will, in fact, be α and will often overestimate the absorption rate constant by more than a factor of 2.

This error in assigning the α-value as the absorption rate constant will occur no matter what calculation method is utilized if no data from other experiments are available (*e.g.*, intravenous studies or studies with drug delivery systems having a markedly different absorption rate). Data points measured after low absorption rates (close to β) will appear to follow a one-compartment model. Although the percent error in calculation of the absorption rate constant may be relatively large, evaluation of the relative rank order of absorption rates will be correct even when the one-compartment model is chosen instead of the correct two-compartment model.

Table II—Comparison of Actual Absorption Rate Constant Ratios for Two-Compartment Data with Ratios Obtained when Data Are Analyzed According to a One-Compartment Model, Utilizing Input and Output Values Given in Table I

k_{a2x}	k_{a2y}	Input Ratio, k_{a2x}/k_{a2y}	Output Ratio, k_{a1x}/k_{a1y}	Error, %
7.2	5.4	1.33	1.84	38.3
7.2	3.6	2.00	3.44	72.0
7.2	1.8	4.00	10.04	151.0
7.2	0.6	12.00	23.55	96.3
5.4	3.6	1.50	1.87	24.7
5.4	1.8	3.00	5.47	82.2
5.4	0.6	9.00	12.82	42.4
3.6	1.8	2.00	2.92	46.1
3.6	0.6	6.00	6.85	14.2
1.8	0.6	3.00	2.34	−21.8

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ACKNOWLEDGMENTS AND ADDRESSES

Received September 25, 1975, from the *School of Pharmacy, University of Connecticut, Storrs, CT 06268, and the ‡Department of Pharmacy, School of Pharmacy, University of California, San Francisco, CA 94143.

Accepted for publication March 24, 1976.

Presented in part at the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, San Francisco meeting, March 1971.

Supported in part by Program Project Grant GM 16496 and Training Grant GM 00728 from the National Institutes of Health. Dr. Ronfeld is grateful for the support he received as a Fellow of the American Foundation for Pharmaceutical Education and as an NIH Predoctoral Fellow.

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