Critical Analysis of "Flip-Flop" Phenomenon in Two-Compartment Pharmacokinetic Model

PETER R. BYRON and ROBERT E. NOTARI ˣ

Abstract □ Computer simulations were used to examine the effect of first-order absorption on the disposition of one- and two-compartment model drugs. Two-compartment systems that attain a clinically acceptable β-phase after rapid intravenous injection were perturbed by introduction of drug *via* first-order absorption. The validity of perceiving such a system as a potential "flip-flop" model was tested by comparing the negative slopes of log-linear plasma–time profiles to known values for k_a and β for various values of k_a, k_{12}, k_{21}, and k_{10}. Although most log-linear plots showed excellent correlation coefficients ($r^2 > 0.996$), their negative slopes (S) did not represent either k_a or β under various combinations. A similar consideration of the one-compartment model enabled a comparison to be made between the two systems. Maximum negative errors were observed for both one- and two-compartment drugs as $k_a \rightarrow k_2$ or β, respectively. The value for S provided a good estimate of the absorption rate constant, k_a, when $k_2 \geq 2k_a$ (one compartment) or $\beta \geq 2k_a$. The elimination rate constant (k_2 or β) could be obtained from S for all one-compartment and some two-compartment drugs when the value of k_a was approximately twice that of k_2 or β. Large positive errors also were observed with certain two-compartment drugs where the ratio of the four rate constants apparently linearized a nonlinear plasma profile. Conditions wherein S may be expected to approach β wherein S approaches k_a are clearly defined.

Keyphrases □ Pharmacokinetic models, two compartment—equation derived for time required for constancy of drug fraction in Compartment 1, effect of absorption and elimination rate constants □ Models, pharmacokinetic—equation derived for the time required for constancy of drug fraction in Compartment 1, effect of absorption and elimination rate constants □ Drug disposition—two-compartment open model, equation derived for time required for constancy of drug fraction in Compartment 1

Distribution and elimination kinetics of a number of drugs can be described by the two-compartment open model shown in Scheme I. Methods were discussed previously (1) for calculating the first-order rate constants, k_{12}, k_{21}, and k_{10}, from blood level data after rapid intravenous injection. Biological half-life, $t_{0.5}$, is commonly estimated from the terminal negative slope (β_{app}) of a first-order plot of plasma concentration using:

$$t_{0.5} = 0.693/\beta_{app} \qquad \text{(Eq. 1)}$$

Reliable estimates are obtained if the fraction of drug in Compartment 1:

$$f_1 = \{(\text{amount})_1/[(\text{amount})_2 + (\text{amount})_1]\}_t \qquad \text{(Eq. 2)}$$

achieves a relatively constant value following intravenous bolus administration. It can easily be shown that f_1 approaches a constant value at its limit, $t \rightarrow \infty$, where:

$$\lim (f_1)_{t \rightarrow \infty} = \beta/k_{10} \qquad \text{(Eq. 3)}$$

and that certain combinations of values of k_{12}, k_{21}, and k_{10} can prolong the time to approach the β-phase.

In this study, an equation was derived to estimate the time required to achieve a "clinically acceptable" degree of constancy for f_1 wherein the value for β_{app} approaches the theoretical value for β. The influence of the relative values of the first-order rate constants upon this time was investigated.

Several reviews (2–4) tabulating $t_{0.5}$ values for numerous commonly used drugs included estimates obtained after extravascular drug administration. Scheme I may be modified to include first-order input to Compartment 1 at a rate described by a first-order absorption rate constant, k_a. In this model, the calculation of half-lives from the terminal log-linear negative slope (S) assumes that $S \rightarrow \beta$.

If absorption is rate limiting, then S is purported to approach k_a (5), a phenomenon commonly known as "flip-flop." This impression is based on the behavior of consecutive first-order reactions ($A \rightarrow B \rightarrow C$), where log-linear plots for the concentration of B can be used to determine the rate constant for the rate-determining step (6). This investigation was designed to determine the errors that could be incurred when β or k_a was estimated by linear regression after extravascular drug administration, using the flip-flop assumption.

EXPERIMENTAL

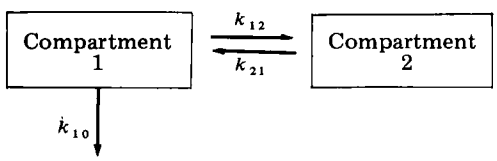
Time to Reach β-Phase after Intravenous Administration—A typical time profile for a drug administered by rapid intravenous injection and described by Scheme I is illustrated in Fig. 1*a*. The time profile for the fraction of *dose* in Compartment 1, F_1, is seen to parallel that in Compartment 2, F_2, after time, t_d, at which time the total body content, $F_1 + F_2$, also becomes linear and parallel. That fraction of *drug in the body* that is contained in Compartment 1, f_1, approaches a constant value at t_d.

Data for drug in the central compartment may be described by:

$$F_1 = F_A e^{-\alpha t} + F_B e^{-\beta t} \qquad \text{(Eq. 4)}$$

where the estimation of values for F_A, α, F_B, and β by the feathering method is illustrated in Fig. 1*b*. Since the time course representing F_1 is the sum of two exponentials, it is possible to estimate the distribution time, t_d, by choosing some arbitrary minimum contribution by the first term, $F_A e^{-\alpha t}$. Therefore, it is possible to solve for the time, t_d, at which the contribution of $F_A e^{-\alpha t}$ becomes equal to some small fraction, P, of $F_B e^{-\beta t}$. When P is sufficiently small, then $F_1 \rightarrow F_B e^{-\beta t}$. Thus, to calculate the time where $F_A e^{-\alpha t}$ is 1% of $F_B e^{-\beta t}$ or:

$$P = F_A e^{-\alpha t}/F_B e^{-\beta t} = 0.01 \qquad \text{(Eq. 5)}$$



Scheme I

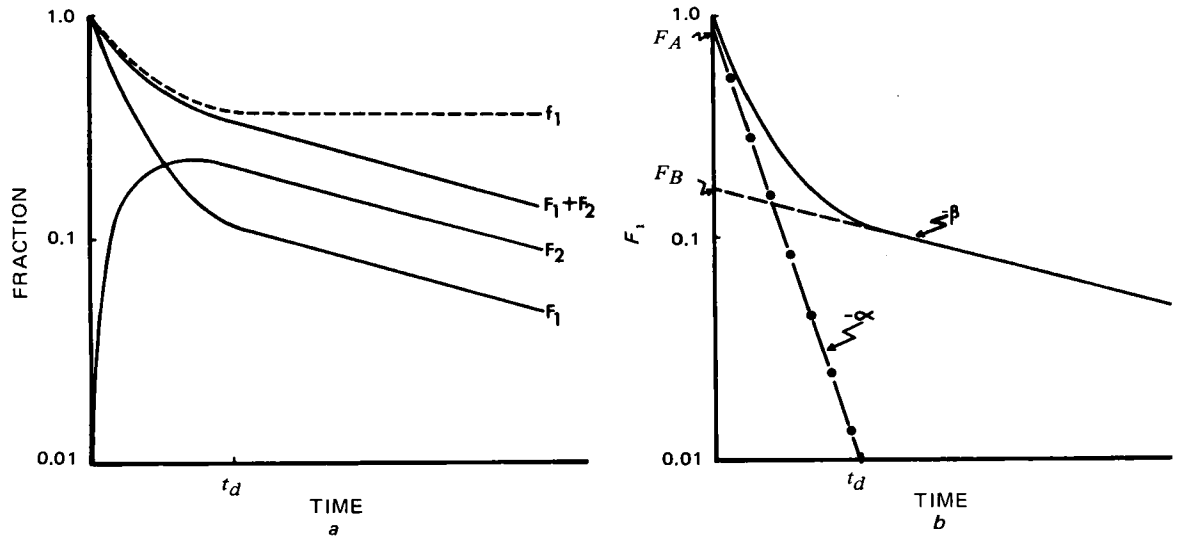


Figure 1—(a) *Dose fraction* (F)*–time profiles for a two-compartment drug after intravenous administration. Dashed line shows* $f_1 = [F_1/(F_1 + F_2)]$ *approaching a constant value at time* t_d. (b) *Graphical estimation of* F_A, α, F_B, *and* β *for a two-compartment drug.*

it is necessary only to rearrange and solve for t_d according to:

$$t_d = [\ln P - \ln (F_A/F_B)]/(\beta - \alpha) \quad \text{(Eq. 6)}$$

This equation may also be rewritten in terms of the first-order rate constants since the ratio, F_A/F_B, may be defined:

$$R = F_A/F_B = (k_{21} - \alpha)/(\beta - k_{21}) \quad \text{(Eq. 7)}$$

Equation 6 may then be simplified to:

$$t_d = [\ln (P/R)]/(\beta - \alpha) \quad \text{(Eq. 8)}$$

which, for the case where $P = 0.01$, may be written:

$$t_d = (4.6 + \ln R)/(\alpha - \beta) \quad \text{(Eq. 9)}$$

Negative Slope of Plasma Level Curve with First-Order Input—The negative slope of the log-linear plasma profile was calculated for values of the constants k_a, k_{12}, k_{21}, and k_{10} by iterative digital computer simulation using Eq. 10 (two-compartment model) and Eq. 11 ($A \xrightarrow{k_a} B \xrightarrow{k_2} C$), which can be found in many texts:

$$F_1 = k_a \{[(k_{21} - k_a)/(\alpha - k_a)(\beta - k_a)]e^{-k_a t} + [(k_{21} - \alpha)/(k_a - \alpha)(\beta - \alpha)]e^{-\alpha t} + [(k_{21} - \beta)/(k_a - \beta)(\alpha - \beta)]e^{-\beta t}\} \quad \text{(Eq. 10)}$$

$$F_1 = \{k_a/(k_2 - k_a)\}[e^{-k_a t} - e^{-k_2 t}] \quad \text{(Eq. 11)}$$

The program was designed to simulate plasma analysis as it is commonly practiced. It begins by finding $(F_1)_{max}$, t_{max}, and t_2, where t_2 corresponds to $0.1(F_1)_{max}$. Subsequently, three sets of eight data points were calculated beginning at $(t_{max} + I)$, $(t_{max} + 2I)$, or $(t_{max} + 3I)$ and separated by a time increment I, where $I = (t_2 - t_{max})/8.0$. Linear regressions of ln F_1 *versus* time enabled an assessment of the correlation coefficients and a comparison of the slopes with theoretical values for β and the absorption rate constant, k_a.

In many cases, obvious nonlinearity was apparent when F_1 values calculated for $t < (t_{max} + 3I)$ were included in the regression analyses. To maintain uniformity, therefore, the negative log-linear slopes quoted throughout this paper are those beginning at $t_1 = (t_{max} + 3I)$ and ending at $t_3 = (t_2 + 2I)$. Simultaneous use of Eq. 9 enabled the prediction of t_d after intravenous administration. The values of k_a, k_{12}, and k_{21} were varied from 0 to 40. In the case of k_{10}, values ranged from 0 to 100.

RESULTS AND DISCUSSION

Time to Reach β-Phase after Intravenous Administration—To evaluate the effect of first-order absorption on drug disposition, it was necessary first to determine the time, t_d, to achieve distribution following rapid intravenous injection (Eq. 9). Very large values for t_d may preclude the clinical assessment of terminal blood level data since the plasma concentration will fall below assayable limits.

The effect of variation of the constants k_{12}, k_{21}, and k_{10} on the time (t_d in half-lives) taken to approach an acceptable β-phase after intravenous administration is summarized in Fig. 2. It is readily apparent that t_d is extremely sensitive to changes in k_{12} as compared to the other constants. As k_{12} decreases relative to k_{21} and k_{10}, t_d increases dramatically. For example, Eq. 9 may be used to predict a t_d value when the ratio k_{12}:k_{21}:k_{10} is 1:40:40. Let us assume that the actual values (in hours^{-1}) are 0.01:0.40:0.40. The calculated value for t_d ($P = 0.01$) would be 37.5 hr (or 18.75 half-lives).

Plasma level data under clinical conditions probably would be assumed to be monoexponential for such a case. In actual fact, the data would be nonlinear, but it would be very difficult to detect this due to biological variation. The apparent value for $t_{0.5}$ might be estimated as 1.78 hr whereas the value calculated from β is 2.0 hr. The reason for this near agreement follows. The fraction of the *dose* in Compartment 2, F_2, at its maximum (where $dF_2/dt = 0$) is described by:

$$(F_2)_{max} = F_1' k_{12}/k_{21} \quad \text{(Eq. 12)}$$

where F_1' = the value for F_1 at the time when $F_2 = (F_2)_{max}$.

The fraction of the *total body content* contained in Compartment 2 when $F_2 = (F_2)_{max}$ may be defined as:

$$(f_2)_{(F_2)_{max}} = (F_2)_{max}/[F_1' + (F_2)_{max}] = k_{12}/(k_{12} + k_{21}) \quad \text{(Eq. 13)}$$

The inset in Fig. 2 illustrates the effect of k_{12} on three parameters, t_d, $(f_2)_{(F_2)_{max}}$, and $(f_2)_\infty$, where:

$$(f_2)_\infty = 1 - (\beta/k_{10}) \quad \text{(Eq. 14)}$$

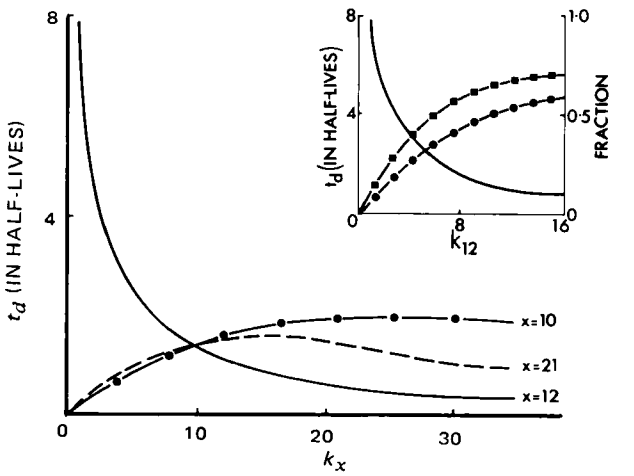


Figure 2—*Effect of* k_{12}, k_{21}, *and* k_{10} *on the distribution time,* t_d *(*x = *12,* $k_{21} = k_{10} = 10$; x= *21,* $k_{12} = k_{10} = 10$; x = *10,* $k_{12} = k_{21} = 10$*). The inset shows the effect of* k_{12} *on: (—)* t_d, *(●)* $(f_2)_{(F_2)_{max}}$, *and (■)* $(f_2)_\infty$.

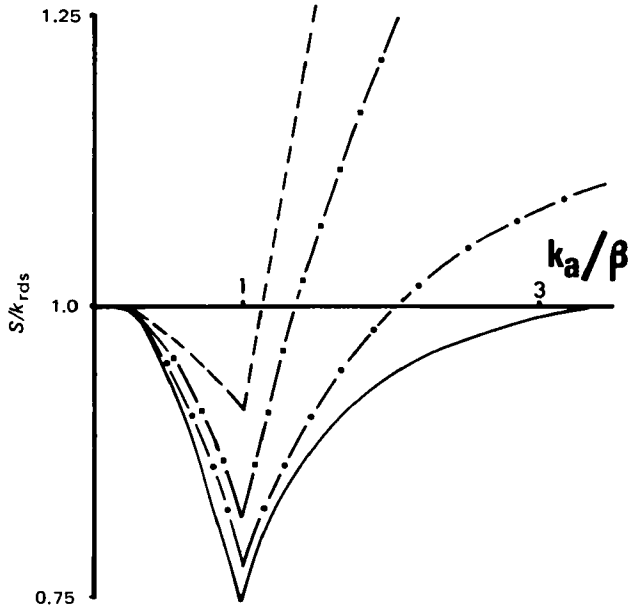


Figure 3—*Ratios of* S/k_a, $(k_a/\beta) < 1$, *and* S/β, $(k_a/\beta) > 1$, *for the cases:* (—) $[k_{10}/(k_{12} = k_{21})] = 0.5$, (●) $[k_{10}/(k_{12} = k_{21})] = 1.5$, (■) $[k_{10}/(k_{12} = k_{21})] = 3.5$, *and* (- -) $[k_{10}/(k_{12} = k_{21})] = 10$.

The inset shows that as the time to approach the β-phase, t_d, increases due to $k_{12} \rightarrow 0$, the fraction in Compartment 2 also approaches zero. Thus, the error incurred in regarding the data as monoexponential decreases at t_d increases. In the limiting case, as $k_{12} \rightarrow 0$, $(f_2)_t \rightarrow 0$ and $\beta \rightarrow k_{10}$, so that monoexponential data result.

Negative Slope (S) of Log-Linear Plasma Level Curve with First-Order Input—Estimating $t_{0.5}$ from plasma level data requires the negative slope of the log-linear plot to approach the value for the first-order rate constant for whole body elimination, *i.e.*, $S \rightarrow \beta$. The phenomenon of flip-flop, a well-recognized occurrence in pharmacokinetics, is assumed due to the absorption rate becoming the rate-determining step (rds) in drug elimination. The value of S was compared to k_a when $(k_a/\beta) < 1$ and to β when $(k_a/\beta) > 1$ for some 2000 computer-generated log-linear plasma profiles defined by the values of k_a, k_{12}, k_{21}, and k_{10}.

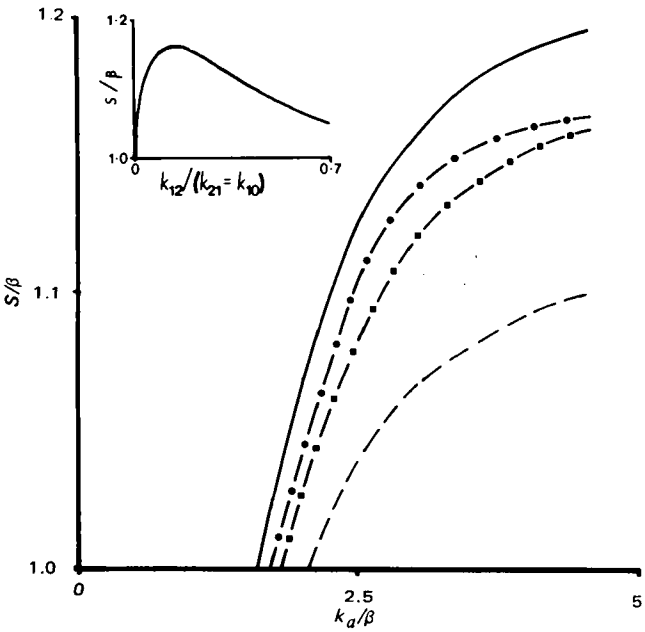


Figure 4—*Relationship of* S *to* β *for the cases:* (●) $[k_{12}/(k_{21} = k_{10})] = 0.05$, (—) $[k_{12}/(k_{21} = k_{10})] = 0.1$, (■) $[k_{12}/(k_{21} = k_{10})] = 0.3$, *and* (- -) $[k_{12}/(k_{21} = k_{10})] = 0.5$. *Inset shows* S/β versus $k_{12}/(k_{21} = k_{10})$ *when* $k_a/\beta = 3$.

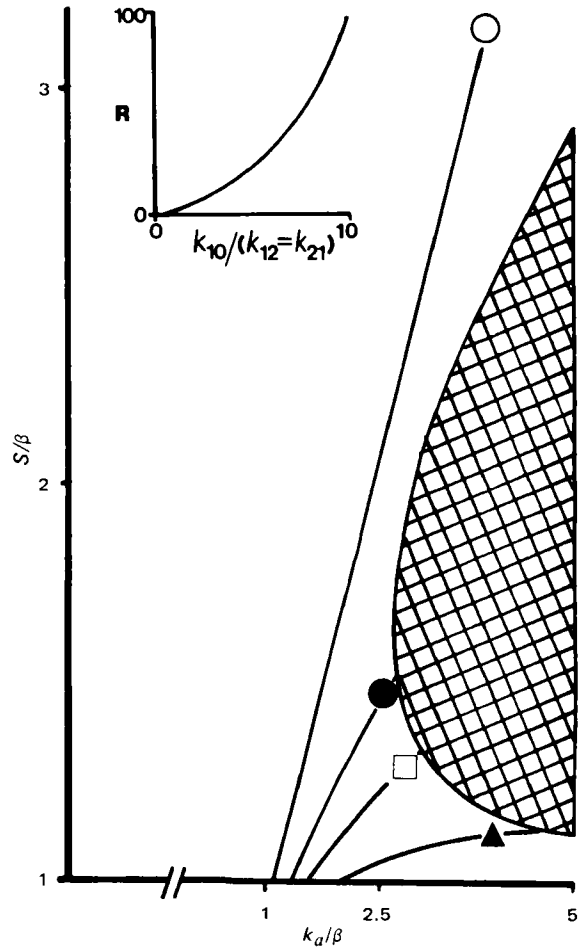


Figure 5—S/β versus k_a/β *for the cases:* (○) $[k_{10}/(k_{12} = k_{21})] = 10$, (●) $[k_{10}/(k_{12} = k_{21})] = 3.5$, (■) $[k_{10}/(k_{12} = k_{21})] = 2.5$, *and* (▲) $[k_{10}/(k_{12} = k_{21})] = 1.5$. *Cross-hatched area represents a zone of nonlinearity where* $r > -0.998$. *Inset plot shows the relationship between* $R = (F_A/F_B)$ *and* $[k_{10}/(k_{12} = k_{21})]$.

Figure 3 shows typical examples of S/k_{rds} ratios for the cases where $k_{12} = k_{21}$ and k_a and k_{10} are varied. The concept of flip-flop was rigorously examined in terms of such diagrams by varying k_a, k_{12}, k_{21}, and k_{10}. In Fig. 3, maximum negative errors are defined by the k_a/β ratio of unity where neither absorption nor elimination is rate limiting. When $(k_a/\beta) < 1$, then $S/k_{rds} \rightarrow 1$ and $S \rightarrow k_a$. Conversely, if $(k_a/\beta) > 1$, elimination may become rate determining and $S \rightarrow \beta$. If $k_{10} > (k_{12} = k_{21})$, however, then S/k_{rds} may become greater than unity at some point defined by the relative values of k_{10} and k_a to k_{12} and k_{21}. In these cases where $(S/k_{rds}) > 1$, a positive error would be made when estimating β from the value of the terminal slope (S).

In all cases discussed, least-squares regression analyses of ln F_1 *versus* t yielded correlation coefficients of $r < -0.998$ ($r^2 > 0.996$).

Negative Errors—The solid line of Fig. 3 represents the negative errors, $(S/k_{rds}) < 1$, incurred in the estimation of β or k_a from the negative slope of log-linear plasma profiles. Purely negative errors were observed only when $k_{12} > (k_{21} = k_{10})$, $k_{21} > (k_{12} = k_{10})$, or $k_{10} < (k_{21} = k_{12})$. The point of the minimum S/k_{rds} ratio is defined by a k_a/β ratio of unity since both k_a and β have the same percentage error when compared to S. At this point, neither absorption nor elimination is rate limiting. The percentage error becomes smaller as the k_a/β ratio is increased from unity ($S \rightarrow \beta$ as $S/k_{rds} \rightarrow 1$). Calculation of S for a one-compartment model using Eq. 11 for a variety of k_a/k_2 ratios yields a plot of S/k_{rds} *versus* k_a/k_2, which is identical to the solid line plot of Fig. 3. The terminal slope, S, may be used to estimate the values of k_a or β (or k_2) within 5% of their true values when $[0.5 > (k_a/\beta) > 2.1]$ or $[0.5 > (k_a/k_2) > 2.1]$.

The dashed lines in Fig. 3, however, show typical effects of variation in the k_{12}:k_{21}:k_{10} ratio outside the conditions of purely negative error defined previously. If the k_a/β ratio is increased still further, then S/β also increases to values well above unity. In these cases, which will be

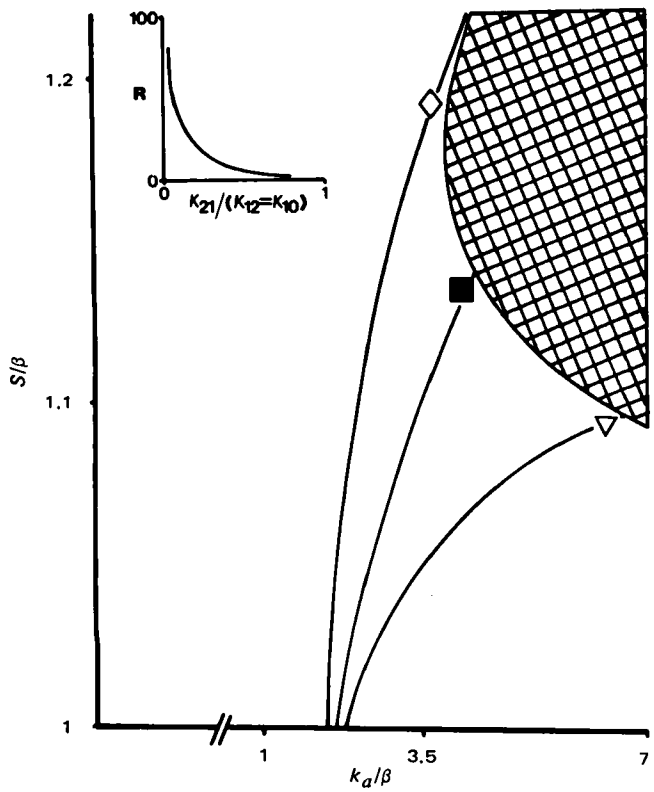


Figure 6—S/β versus k_a/β *for the cases:* (◇) $[k_{21}/(k_{12} = k_{10})] = 0.05$, (□) $[k_{21}/(k_{12} = k_{10})] = 0.2$, *and* (▽) $[k_{21}/(k_{12} = k_{10})] = 0.5$. *Cross-hatching represents nonlinearity* ($r > -0.998$). *Inset shows* R = (F_A/F_B) versus $[k_{21}/(k_{12} = k_{10})]$.

discussed more fully in the following section, a k_a/β ratio exists at which the correct value for β may be obtained from S for entirely fortuitous reasons.

Positive Errors Due to Effect of t_d—Positive errors in the estimates for $\beta(S > \beta)$ are observed in cases where k_{12} approaches relatively small values. Figure 4 shows examples of typical S/β ratios when $k_{21} = k_{10} = 10$ while k_{12} and k_a/β are varied from 0.5 to 5. The inset plot of Fig. 4 demonstrates that when the k_a/β ratio is held constant, $(k_a/\beta) = 3.0$, and $k_{12} = 1.5$, a position of maximum positive error occurs at $(S/\beta) = 1.16$. This effect can be attributed to slow distribution.

Following intravenous administration (Fig. 2), the distribution time, t_d, is greater than 3.8 half-lives when $[k_{12}/(k_{21} = k_{10})] < 0.3$. Thus, when $[k_{12}/(k_{21} = k_{10})] = 0.15$ and $k_a/\beta = 3$ at the position of maximum positive error (Fig. 4 inset), a similar overestimate of β would probably be made from intravenous data.

Positive Errors Due to Effect of F_A/F_B Ratio—Figures 5 and 6 show the relationship between S/β and k_a/β for the cases $k_{10} > (k_{12} = k_{21})$ and $k_{21} < (k_{12} = k_{10})$. It is readily apparent from the inset plots of F_A/F_B *versus* $[k_{10}/(k_{21} = k_{12})]$ and $[k_{21}/(k_{12} = k_{10})]$ that the S/β ratio increases with either decreasing k_{21} or increasing k_{10} if k_a/β is held constant. In cases where $[k_{10}/(k_{12} = k_{21})] > 8$, plots always appeared linear ($r < -0.998$) irrespective of the k_a/β ratio.

Intravenous and oral plots are shown for $[k_{10}/(k_{12} = k_{21})] = 10$ in Fig. 7*a*. After intravenous bolus administration, the α-slope might mistakenly be used to calculate the $t_{0.5}$ of the drug unless the plasma was sampled through at least 2.5 log cycles. However, administration by first-order absorption ($k_a/\beta = 3.9$) shows how k_a can apparently linearize plasma decay. This negative slope, S, approaches neither the α nor β value between t_1 and t_3. If linearity were accepted as the criterion for $S \rightarrow \beta$, then the $t_{0.5}$ estimate would be less than half the theoretical value.

In contrast to the previous case, Fig. 7*b* shows an example where it is more likely that a correct estimate for β would be made after intravenous administration ($F_A/F_B = 10.9$). Administration by first-order absorption, however, shows the pronounced influence of k_a upon the negative slope, S, $(k_a/\beta) = 2.65$. A 39% overestimate can be made in β by accepting linearity as an indication that $S \rightarrow \beta$. The cross-

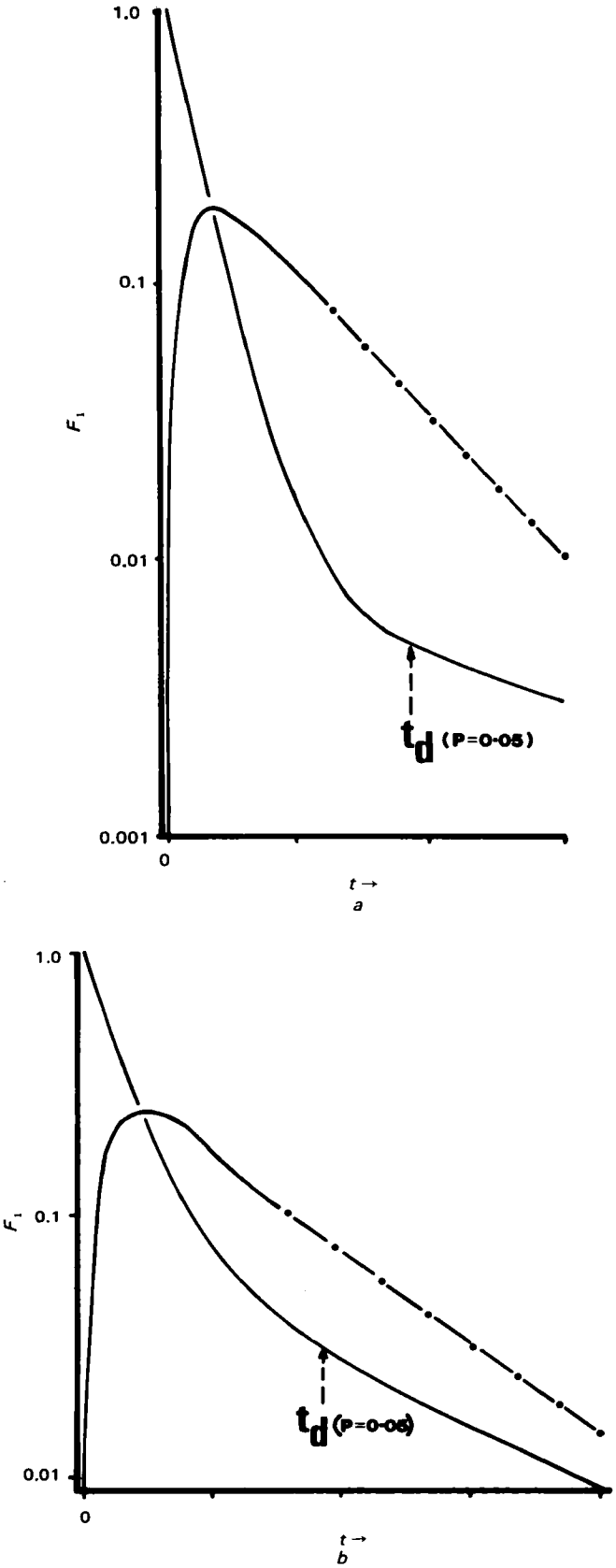


Figure 7—*Comparison of intravenous and oral log-linear plasma profiles for the cases:* (a) $[k_{10}/(k_{12} = k_{21})] = 10$, $k_a/\beta = 3.9$; *and* (b) $[k_{10}/(k_{12} = k_{21})] = 3$, $k_a/\beta = 2.65$.

hatched area in Fig. 5, where $[k_{10}/(k_{12} = k_{21})] = 3$, clearly demonstrates that as k_a/β is increased still further, the t_1–t_3 portion of the oral plot approaches obvious nonlinearity ($r > -0.998$).

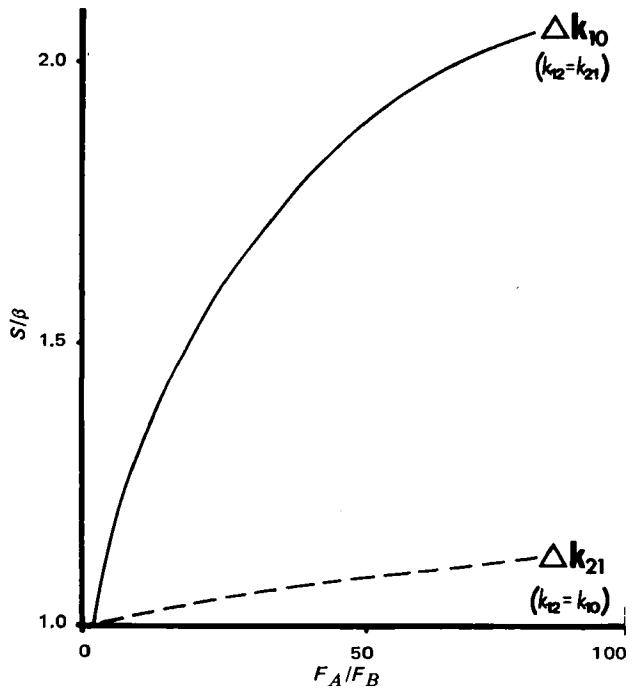


Figure 8—*Relationship between* S/β *and* F_A/F_B *shown at a constant* k_a/β (= 2.5) *by variation of* k_{10} *and* k_{21} (*solid and dashed lines, respectively*).

The errors shown in Figs. 5 and 6, therefore, were attributed directly to the observation of α-phase data which can be apparently linearized during the time period t_1–t_3 over a wide range of k_a/β values. Figure 8 shows that F_A/F_B ratios alone do not predict the positive errors in estimating β from S values. Thus, positive errors in β estimates are, in fact, specific to the k_a:k_{12}:k_{21}:k_{10} ratio and are not predictable solely by consideration of F_A/F_B.

CONCLUSIONS

It is well recognized that the negative terminal slopes of log-linear plots of plasma drug concentration following oral administration may not represent reasonable estimates for the first-order elimination constant, β. In cases where the value of the slope is less than the intravenous estimate for β, it generally has been concluded that absorption is rate limiting and that the slope reflects the absorption rate constant. The results clearly demonstrate the frailty of this assumption for both one- and two-compartmental model drugs. In fact, β (or k_2) must have at least twice the value of the absorption rate constant before a reasonable estimate of k_a can be made from the negative slope, S.

It also was reported in the literature that in certain cases the value for S is apparently too large following oral administration. The significant decrease of estimates made from slopes during the steady state as compared to values from single oral doses (7) is perhaps the most widely discussed example (4, 6–8). It was suggested that the single oral dose values represent the influence of distribution (4). The present study demonstrates that S following oral administration can indeed be larger than β due to the apparent linearization of α-phase data at certain k_a/β ratios.

Thus, it is possible to obtain all of the following: good estimates for k_a or β; negative errors in the estimates for k_a; and both negative and positive errors in the estimates for β depending on the relative values for k_a, k_{12}, k_{21}, and k_{10}.

REFERENCES

(1) S. Riegelman, J. C. K. Loo, and M. Rowland, *J. Pharm. Sci.*, **57**, 117(1968).

(2) T. R. Simpson and J. P. Juergens, *Hosp. Pharm.*, **8**, 68(1973).

(3) W. A. Ritschel, *Drug Intel. Clin. Pharm.*, **4**, 332(1970).

(4) J. M. Van Rossum, in "Drug Design," vol. 1, E. J. Ariens, Ed., Academic, New York, N.Y., 1971, pp. 472, 509.

(5) J. T. Doluisio, J. C. La Piana, and L. W. Dittert, *J. Pharm. Sci.*, **60**, 715(1971).

(6) R. E. Notari, "Biopharmaceutics and Pharmacokinetics, An Introduction," 2nd ed., Dekker, New York, N.Y., 1975, pp. 86, 200.

(7) J. T. Doluisio and L. W. Dittert, *Clin. Pharmacol. Ther.*, **10**, 690(1969).

(8) M. Gibaldi and H. Weintraub, *J. Pharm. Sci.*, **60**, 624(1971).

ACKNOWLEDGMENTS AND ADDRESSES

Received August 20, 1975, from the *Pharmaceutics Research Group, University of Aston in Birmingham, Gosta Green, Birmingham, B4 7ET, England.*

Accepted for publication October 8, 1975.

[x] To whom inquiries should be directed. Present address: College of Pharmacy, Ohio State University, Columbus, OH 43210