internal standard (hydrocortisone) and III was obtained (Fig. 3C) in the chromatogram.

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A Time-Lag Model for Pharmacokinetics of Drugs Subject to Enterohepatic Circulation

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Abstract □ A two-compartment model with time lag is proposed to describe the pharmacokinetics of drugs subject to enterohepatic circulation. The basic model, including two compartments for body and GI tract, respectively, with elimination occurring from both compartments, was previously proposed. The assumption that the reabsorption of a drug molecule is delayed after its biliary excretion is expressed by the addition of a time lag in the transfer from the first to the second compartment. Computer simulation of the model for intravenous bolus injection and oral intake of the drug was performed through first-order numerical integration. Several qualitative results concerning changes in pharmacokinetics due to modifications in biliary excretion, in reabsorption, or in elimination are identical with predictions using the basic model. However, several qualitative and quantitative results were significantly different. The pharmacokinetics, though remaining linear, are no longer biexponential. Initial decay after intravenous injection was not affected by modifications in reabsorption or elimination from intestine. Predictions based on the time-delay model agree with existing experimental evidence concerning pharmacokinetics of substances undergoing enterohepatic cycling. Delayed recirculation may lead to rebounds in plasma level profiles as well as after intravenous and oral administration. The half-life of the drug is significantly prolonged even when the kinetic processes involved in recirculation remain unchanged.

Keyphrases □ Pharmacokinetics—time-lag model, enterohepatic drug circulation □ Models, pharmacokinetic—enterohepatic drug circulation, time-lag model □ Enterohepatic circulation—drugs, pharmacokinetics, time-lag model

When a substance is taken up by the liver and excreted into the bile, it may be either eliminated through the GI tract or reabsorbed and carried to the liver *via* the portal blood stream. This second process is known as enterohepatic cycling. This phenomenon affects both endogenous and exogenous substances.

BACKGROUND

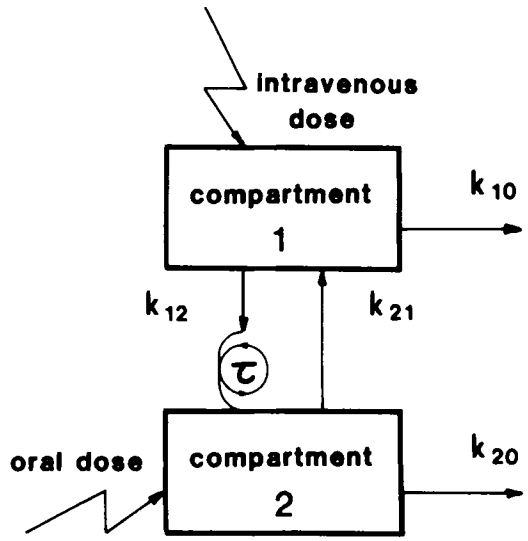
A two-compartment model was previously developed (1) representing the body and the GI tract. Qualitative modifications in pharmacokinetic time-profiles and parameters for drugs subject to enterohepatic cycling due to changes in biliary excretion and reabsorption rates are well depicted by this model.

Predictions of the two-compartment model agree with previous experimental results (1, 2). However, some discrepancies, such as the evidence of a secondary peak in the time course of serum concentrations, remain. Such a secondary peak was reported (3) appearing after intravenous, oral, and intraportal administration of morphine in rats. An eight-compartment model for morphine pharmacokinetics was proposed. The GI tract compartment of Harrison and Gibaldi (1) is split into a catenary system of three compartments forming a loop connected with the central compartment. Experimental evidence for a secondary peak in plasma radioactivity time profiles, as well as subsequent very slow elimination kinetics exist for labeled vitamin D_3 in humans (4) and rats (5). The main active metabolite of vitamin D_3 undergoes enterohepatic cycling (6).

A modification of the two-compartment enterohepatic recirculation model is proposed to take into account these previous experimental findings. The basic assumption is that a time-delay exists between the excretion of a given molecule of the substance into bile and its reabsorption from the intestine. This time lag may be due to delayed biotransformation in the liver, to the storage of the substance in the gallbladder (*e.g.*, in humans), or simply to its transport in bile, at a limited flow-rate, from the site of excretion to the site of reabsorption. The corresponding time-delay model proposed here exhibits qualitative agreement with the two basic observations on pharmacokinetics of drugs subject to enterohepatic circulation: first, the occurrence of "rebounds" in serum level profiles after intravenous and oral administration of drug; and second, the slow terminal kinetics of the drug when recirculation occurs, even when the processes of deconjugation and reabsorption are not rate-limiting.

THEORETICAL

Mathematical Formulation—The model presented in Scheme I is a two-compartment system differing from the basic model of Harrison



Scheme I—Time-lag pharmacokinetic model for a drug subject to enterohepatic circulation. Compartment 1 represents the body including the liver. Compartment 2 represents the GI tract. Existence of a time delay is assumed after biliary excretion, before reabsorption can occur.

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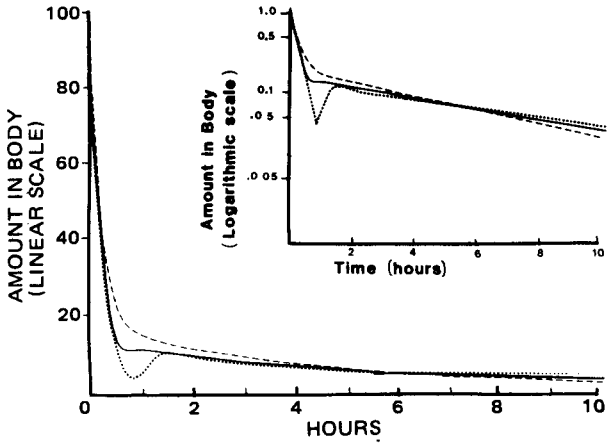

Figure 1—*Effect of time lag on pharmacokinetic profile after intravenous injection. For all curves,* $k_{12} = 3.0$, $k_{10} = 1.0$, $k_{21} = 1.0$, *and* $k_{20} = 0.0\ hr^{-1}$. *Key: - - -,* $\tau = 0$ *(no time lag);* ——, $\tau = 0.4$ *hr; and . . .,* $\tau = 0.8$ *hr.*

and Gibaldi (1) by the addition of a time lag on the transfer pathway from compartment 1 to compartment 2. In this model, compartment 1 represents the whole body, including the liver, while compartment 2 describes the GI tract.

The transfer processes are supposed to be governed by first-order kinetics and are denoted respectively by k_{10} for the nonbiliary elimination process, k_{20} for the biotransformation in the GI tract and the fecal excretion, and k_{21} for the reabsorption process.

The important characteristic of the model lies in the addition of a time delay occurring in series with the conventional k_{12} coefficient, thus implying that the drug leaving compartment 1 at time t enters compartment 2 at time $t + \tau$.

The corresponding mathematical formulation is:

$$\frac{dA_1(t)}{dt} = -(k_{10} + k_{12})A_1(t) + k_{21}A_2(t) \qquad \text{(Eq. 1}a\text{)}$$

$$\frac{dA_2(t)}{dt} = -(k_{20} + k_{21})A_2(t) + k_{12}A_1(t - \tau) \qquad \text{(Eq. 1}b\text{)}$$

Due to the existence of this time delay, the initial conditions take a special form; to calculate the solutions of Eqs. 1*a* and 1*b* starting from arbitrary time t_0, one has to define:

$$A_1(t) \text{ for } t_0 - \tau \leq t \leq t_0 \qquad \text{(Eq. 2}a\text{)}$$

and

$$A_2(t) \text{ for } t = t_0 \qquad \text{(Eq. 2}b\text{)}$$

To be more general, it is also possible to account for any input either in compartment 1 or compartment 2 or both by adding appropriate terms in Eqs. 1*a* and 1*b*. In the present study the single intravenous injection of a given dose D of drug, and the single oral intake of the same dose are considered.

In both cases, the mathematical formulation is described by Eqs. 1*a* and 1*b* with the corresponding initial conditions. For intravenous administration:

$$\begin{gathered} A_1(0) = D \\ A_1(t) = 0 \quad \text{for } -\tau \leq t < 0 \\ A_2(0) = 0 \end{gathered} \qquad \text{(Eq. 3)}$$

and for oral administration:

$$\begin{gathered} A_1(t) = 0 \quad \text{for } -\tau \leq t \leq 0 \\ A_2(0) = D \end{gathered} \qquad \text{(Eq. 4)}$$

Simulation of the Model—Two models were studied: model I corresponds to an intravenous single dose and is described by Eqs. 1*a*, 1*b*, and 3; model II corresponds to an oral single dose and is described by Eqs. 1*a*, 1*b*, and 4.

In both cases, the explicit analytical solutions can only be derived in a recurrent manner on successive time intervals. The results obtained for the models on the first two intervals of duration τ are given in the *Appendix*. It must be emphasized that the derived expressions increase in complexity when t gets larger in such a way that they rapidly become intractable in practice.

The simulation of the models, and more generally of Eqs. 1*a* and 1*b* with appropriate input and initial conditions, has to be carried out through numerical integration.

The method proposed in this study is the first-order Euler method, which calculates the values of $A_1(t)$ and $A_2(t)$ at discrete times $t_j = jh$, where h is a small time increment and j is any positive integer; the time lag should also be a multiple integer of h. The corresponding recursive equations are given by:

$$A_1(t_{j+1}) = (1 - hK_1)A_1(t_j) + hk_{21}A_2(t_j) \qquad \text{(Eq. 5}a\text{)}$$

$$A_2(t_{j+1}) = (1 - hK_2)A_2(t_j) + hk_{12}A_1(t_j - \tau) \qquad \text{(Eq. 5}b\text{)}$$

where

$$K_1 = k_{10} + k_{12} \text{ and } K_2 = k_{20} + k_{21}.$$

Sensitivity Study—Theoretical sensitivity analysis of the whole pharmacokinetic profile through partial differentiation of $A_1(t)$ with respect to the parameters is difficult in the present case, since no explicit analytical expression is available for the complete solution. The study of the influence of modifications in the microconstants k_{12}, k_{21}, k_{10}, and k_{20} and in the time lag τ was performed numerically using repeated computer simulations.

The reference parameter values are those used by Harrison and Gibaldi (1), *i.e.*, $k_{12} = 3.0$, $k_{21} = 1.0$, and $k_{20} = 0.0\ hr^{-1}$. Modified values of the microconstants and values of τ, from 0.0 to 1.0 hr, are indicated for each computer simulation under the corresponding figure or in the text.

With respect to terminal kinetics, general algebraic results can be given. Assuming the final phase of the decay is exponential, the terminal rate constant β' is the solution of the following equation, whose derivation is given in the *Appendix:*

$$(\beta')^2 - \beta'(k_{12} + k_{10} + k_{21} + k_{20}) + (k_{12} + k_{10})(k_{21} + k_{20}) - k_{12}k_{21}\exp(\beta'\tau) = 0 \qquad \text{(Eq. 6)}$$

Because of the term $\exp(\beta'\tau)$, Eq. 6 cannot be solved explicitly for β'. Accordingly, values of β' and of the terminal half-life ($T^{\beta'}_{1/2}$) were obtained numerically for each computer-simulated pharmacokinetic profile. Nevertheless, the equation can be used to investigate the dependency of β' on the microconstants and the time lag. Analytical sensitivity study of β' is explained in the *Appendix*.

Note also that for $\tau = 0$, Eq. 6 reduces to the customary equation for determination of α and β for the basic two-compartment open model for enterohepatic circulation without time delay (1, 2). Furthermore, if k_{12} is interchanged with k_{21}, and k_{10} is interchanged with k_{20} at the same time, the equation remains identical. Hence, the value of β' is not modified.

RESULTS

The case where there is no time delay between biliary excretion and drug reabsorption has been studied extensively (1, 2). This presentation is therefore restricted to the case where the time lag is of the same order of magnitude as the time constants of the first-order kinetics accounting for distribution and elimination.

Modifications in the serum level profile due to changes in the time lag τ (all microconstants being unchanged) are presented in Fig. 1. When τ is zero, the amount in the body shows biexponential monotonic decrease. When τ becomes larger, a plateau ($\tau = 0.4$) is obtained first, and for greater values ($\tau = 0.8$) a significant rebound appears in the time profile. Three periods may be distinguished on the pharmacokinetic profile:

1. From zero to τ, the amount in the body decreases monoexponentially (by analogy with conventional notation, the term α'-phase is proposed).
2. When distribution is achieved, the amount in the body again decreases exponentially with constant β' (the β'-phase).
3. Between these two extreme periods, there exists a transient phase where the influence of the time lag is most apparent (τ-phase).

Although the simulated curves displayed in Fig. 1 correspond to maximum enterohepatic cycling ($k_{20} = 0$), the qualitative results remain the same even when the drug is partly eliminated through the intestine ($k_{20} \neq 0$). When a time lag is present, the entire pharmacokinetic profile is modified, in the so-called initial distribution phase as well as in the terminal elimination phase. Further increase in τ gives rise to other peaks in the drug level profile so that the duration of the transient phase becomes longer. Hence, the whole distribution phase (including the α'-phase

and the τ-phase) is time-lag sensitive with respect to its profile and also to its duration. Furthermore, the hybrid constant β', which describes the terminal phase, decreases when τ is enhanced (*Appendix*) regardless of the combination of microconstants. Figure 1 shows how terminal kinetics slow down when the time lag increases. For example, values of $T_{1/2}^{\beta'}$ for $\tau = 0$, $\tau = 0.4$, and $\tau = 0.8$ hr (Fig. 1) are respectively 3.3, 4.2, and 5.1 hr; there is a 50% increase in terminal half-life between the two extreme cases.

The effects of modifications in biliary excretion on the pharmacokinetics of drugs subject to enterohepatic cycling when the basic model ($\tau = 0$) is considered have been described previously (1, 2). Existence of a significant time delay between excretion and reabsorption slightly modifies the conclusions. The decay in the initial phase is slower when k_{12} is reduced, regardless of other parameter values. The influence of modifications in k_{12} on β', and therefore on the terminal half-life $T_{1/2}^{\beta'}$, are less simple. If $k_{20} < k_{10}$, *i.e.*, when nonbiliary elimination from the body is predominant, a decrease in biliary excretion leads to an increase in β', and therefore shortens the half-life of the drug. For the curves displayed in Fig. 2 ($k_{10} = 0.5$, $k_{20} = 0.2$ hr^{-1}), the half-lives are 4.5, 3.1, and 2.2 hr for k_{12} values of 3.0, 1.0, and 0.33 hr^{-1}, respectively. More precisely, an increase in k_{12} will always decrease β' if $k_{20} < k_{10} + \Delta_1$, where Δ_1 (a quantity depending on k_{10}, k_{21}, and τ) is zero for the basic model and strictly positive when a time lag exists (*Appendix*). On the other hand, if $k_{20} > k_{10} + \Delta_1$, *i.e.*, when the intestine plays the dominant role in elimination, the opposite results are obtained. In this case, the reduction in k_{12} leads to the reduction in β'. However, this effect is markedly less than in the first case ($k_{20} < k_{10}$). For the same set of k_{12} values, the values computed for $T_{1/2}^{\beta'}$ when $k_{10} = 0.2$ and $k_{20} = 0.5$ hr^{-1} are 3.0, 3.1, and 3.3 hr, respectively. Regardless of the relative magnitudes of k_{10} and k_{20}, the pharmacokinetic profile becomes increasingly smooth when k_{12} decreases (Fig. 2). However, note that the initial decrease is strictly monoexponential for the duration of the time delay (1.0 hr for these simulations), even when no rebound is apparent.

The influence of reabsorption on drug disposition was analytically studied by Chen and Gross (2). They showed that enhancement in reabsorption (increase in k_{21}) produces the same effects on terminal kinetics as reduction in biliary excretion (decrease in k_{12}); the effect may be an increase or a decrease of the half-life, depending on which of the parameters, k_{10} or k_{20}, is the greatest. Predictions of the time-lag model are identical with those of the basic model when either $k_{10} < k_{20}$ or $k_{10} > k_{20} + \Delta_2$, where $\Delta_2 > 0$ if $\tau > 0$ (*Appendix*). Enhancement of the reabsorption rate k_{21} will increase the half-life in the first case and reduce $T_{1/2}^{\beta'}$ in the second case. However, if k_{10} is such that $k_{20} < k_{10} < k_{20} + \Delta_2$, increased reabsorption will produce a longer, not shorter, half-life. The curves shown in Fig. 3 are associated with parameter values such that the double inequality holds. Terminal half-lives $T_{1/2}^{\beta'}$ are 3.0, 3.1, and 3.3 hr when k_{21} is set equal to 0.33, 1.0, and 3.0 hr^{-1}, respectively. Predictions based on the time-lag model also differ from those of Chen and Gross (2) when the initial decay is considered. The three simulated curves displayed in Fig. 3 are superimposed during the 1st hr. When a time lag is present, the pharmacokinetics after intravenous injection are insensitive to modifications in reabsorption until τ has elapsed. Influence of reabsorption is only apparent in the transient and terminal phase of the pharmacokinetic profile.

Existence of the rebound is independent of the relative magnitude of rate constants k_{12} and k_{21}. It may be observed either with high biliary excretion and moderate reabsorption ($k_{12} = 3.0$, $k_{21} = 1.0$; Fig. 2) or with moderate biliary excretion and high reabsorption ($k_{12} = 1.0$, $k_{21} = 3.0$; Fig. 3). A slight decrease in either k_{12} or k_{21} implies reduction in the amplitude of the peak; further decrease leads to complete disappearance of this peak.

The influence of both elimination processes (*e.g.*, through the kidney and the intestine) was studied through modifications in rate constants k_{10} and k_{20} (Fig. 4). The first extreme case appears when enterohepatic recirculation is complete ($k_{20} = 0$). When k_{10} varies, both α' and β' vary accordingly; however, the transient τ-phase is modified to a lesser extent. The semi-logarithmic diagram (Fig. 4*a*) does not give an entirely satisfactory description of the time process. Although the minimum (A_1 min) and the peak (A_1 max) both occur when k_{10} is reduced, the magnitude of the gap between these two values remains almost constant and is even slightly increased when k_{10} decreases. The second extreme case is when the substance is not subject to nonbiliary elimination from the body ($k_{10} = 0$). When k_{20} varies, the initial decay remains the same; the α'-phase is insensitive to modifications in k_{20} as well as in k_{21} (Fig. 4*b*). In any case, the terminal half-life $T_{1/2}^{\beta'}$ is longer when either k_{10} or k_{20} is reduced, regardless of the other parameters' values (*Appendix*). If elimination occurs through both the kidney and the intestine, the corresponding pharmacokinetic profile is intermediate between the two extremes.

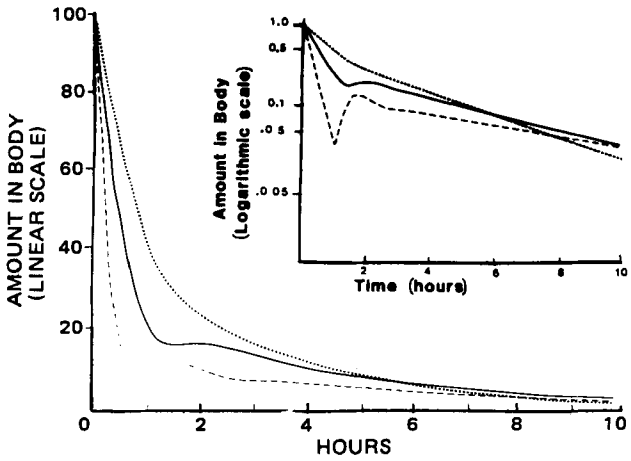

Figure 2—*Effect of biliary excretion on pharmacokinetic profile without modification in time lag. For all curves,* $k_{10} = 0.5$, $k_{21} = 1.0$, $k_{20} = 0.2$ hr^{-1}, *and* $\tau = 1.0$ hr ($k_{20} < k_{10} + \Delta_1$). *Key:* - - -, $k_{12} = 3.0$ hr^{-1}; —, $k_{12} = 1.0$ hr^{-1}; *and* . . ., $k_{12} = 0.33$ hr^{-1}.

The time-delay model may also reveal what happens after oral intake of the drug. The relationship between pharmacokinetic profiles after intravenous and oral administration of a substance is shown in Fig. 5 for the basic model of enterohepatic circulation (1) and the model with time lag ($k_{20} = 0$, $k_{12} > k_{21}$). The oral profile is smoother than the intravenous in both cases. How the increase in time lag affects the pharmacokinetic profile is further depicted in Fig. 6, where $k_{21} > k_{12}$. When the reabsorption rate is greater than the biliary excretion rate, somewhat sharper time profiles (Fig. 6) than in the reverse case are observed. Nevertheless, the conclusions are the same whenever $k_{12} > k_{21}$ (Fig. 5) or $k_{12} < k_{21}$ (Fig. 6). When the delay is present in the enterohepatic cycle, the terminal half-life is prolonged. When τ increases, the τ-phase becomes first apparent ($\tau = 0.4$) and evident afterward ($\tau = 0.8$), although the gap between the local minimum and the secondary peak is less than in the corresponding intravenous case. Furthermore, the customary first peak, though occurring sooner, is of lesser magnitude than in the standard case where no time delay is present.

DISCUSSION

The influence of a delay for drugs subject to enterohepatic circulation was investigated through computer simulation. The time-lag model is a modification of a two-compartment model first proposed by Harrison and Gibaldi (1). Predictions of the time-lag model on the influence of cholestasis on pharmacokinetics show qualitative agreement with results obtained through an analytical parameter sensitivity study of the basic model (2). However, changes in reabsorption or in intestinal elimination lead to different results. The basic model predicts that the α-phase is

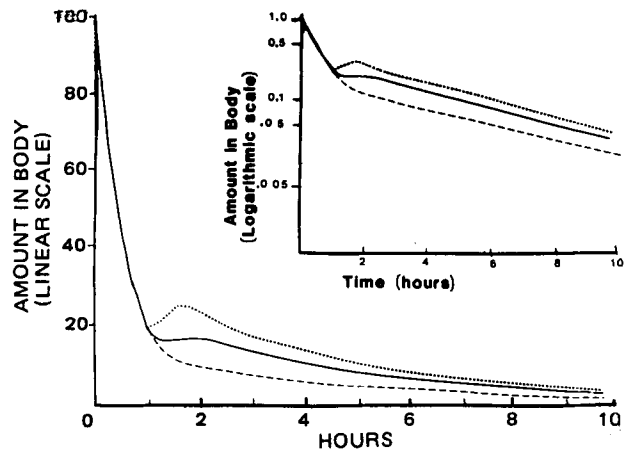

Figure 3—*Effect of reabsorption on pharmacokinetic profile without modification in time lag. For all curves,* $k_{12} = 3.0$, $k_{10} = 0.5$, $k_{20} = 0.2$ hr^{-1}, *and* $\tau = 1.0$ hr ($k_{20} < k_{10} < k_{20} + \Delta_2$). *Key:* . . ., $k_{21} = 3.0$ hr^{-1}; —, $k_{21} = 1.0$ hr^{-1}; *and* - - -, $k_{21} = 0.33$ hr^{-1}.

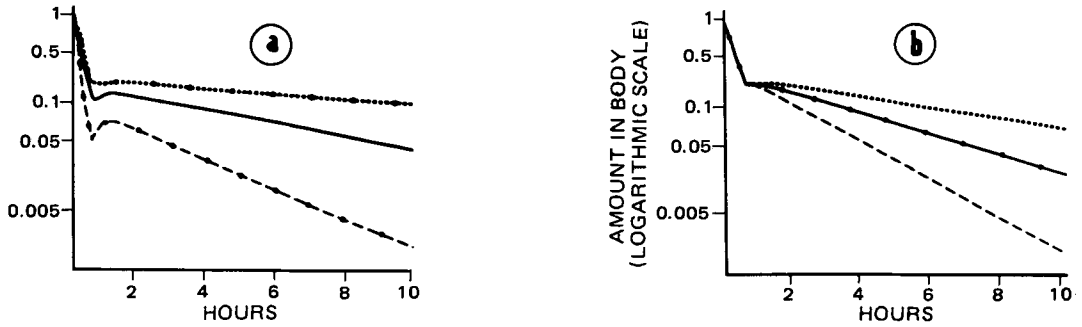

Figure 4—*Effect of both elimination processes on pharmacokinetic profile without modification in time lag. Parameters* k_{12}, k_{21}, *and* τ *are identical for all simulations* ($k_{12} = 3.0$, $k_{21} = 1.0\ hr^{-1}$; *and* $\tau = 0.5\ hr$). *(a) Nonbiliary elimination only* ($k_{20} = 0.0\ hr^{-1}$). *Key:* · ● ·; $k_{10} = 0.33\ hr^{-1}$; —, $k_{10} = 1.0\ hr^{-1}$; *and* –●–, $k_{10} = 3.0\ hr^{-1}$. *(b) Elimination from intestine only* ($k_{10} = 0.0\ hr^{-1}$). *Key:* . . ., $k_{20} = 0.25\ hr^{-1}$, —●—, $k_{20} = 0.50\ hr^{-1}$; *and* - - -, $k_{20} = 1.0\ hr^{-1}$.

modified when either the reabsorption rate k_{21} or the intestinal elimination rate k_{20} changes. Instead, when a significant delay is present in the enterohepatic cycling process, modifications in reabsorption or in intestinal elimination do not affect the initial decay of the plasma level after intravenous injection of the drug.

Further basic differences between both models become apparent when pharmacokinetic profiles are considered after intravenous injection as well as after oral intake of the drug. When a time lag is present, the time profile is not biexponential. For the same values of the microconstants, the time-lag model exhibits both a more rapid decay in the initial phase and a slower disappearance rate for the terminal phase than the basic model. An increase of ~50% in the terminal half-life value is not uncommon for the range of values of microconstants and time lag studied here. In addition to monoexponential initial and terminal kinetics, the time-lag model shows specific behavior in the transient phase. Delayed reabsorption may lead to uncommon patterns such as rebounds, or secondary peaks in plasma level profiles after intravenous injection or oral intake of the drug. Although apparently uncharacteristic, phenomenon of this kind were described for substances undergoing enterohepatic circulation such as morphine (3) and the main metabolite of vitamin D_3 (4–6). The eight-compartment model devised previously to describe morphine pharmacokinetics gives an adequate description of the data (3). It accounts for both rebounds in the measured levels and slow terminal kinetics, two basic features often connected with significant enterohepatic circulation. The overall rate-limiting step in the model (3) is morphine reabsorption from the GI tract; this result may be specific for that drug. In spite of its relative complexity as compared with the eight-compartment model, the time-lag model may produce slow terminal kinetics even when the overall rate-limiting step does not belong to the enterohepatic cycling loop. Existence of a time delay in recirculation prolongs the terminal half-life of the drug by much more than the time lag itself.

Nevertheless, the time-lag model is certainly a rough approximation of the underlying process. A representation of all complex physiological processes involved in enterohepatic circulation of a substance by two first-order rate constants with an additional time lag (presumably due to transport delay) is an oversimplification.

Furthermore, the assumption that the time lag is constant for the duration of the pharmacokinetic experiment may also be an approximation. The delay may be a function of time following slight modifications in bile flow, or may show discontinuous variations in some species due to sudden emptying of the gallbladder. Furthermore, the successive steps of hepatic conjugation, biliary excretion of the metabolite, deconjugation in the GI tract, and reabsorption of the parent drug have been summarized by means of only two first-order rate constants. Although the two-compartment time-lag model is a simplification, it seems to be a reasonable compromise, since it exhibits satisfactory qualitative agreement with existing data.

Enterohepatic recirculation is not the only pharmacokinetic process where time-lag models have been shown to be valuable. Evidence for time-delayed response also exists for various drugs after oral intake. However, pharmacokinetic analysis is somewhat simpler in the latter case because the absorption phase (as opposed to the distribution phase) is affected. Nevertheless, time-lag models may be useful for pharmacokinetic interpretation and substitutes for conventional standard compartment models that fail to describe the data. However, even when a significant time-delay exists, evidence for it may be difficult to demonstrate. Secondary peaks in plasma level profiles may not be observable on all pharmacokinetic data in a series of experiments. Sensitivity analysis of the time-lag model has shown that moderate changes in microconstants and time lag among the sample subjects may lead to important variations in the shapes of time profiles. Predefined standard sampling, a basic requirement in most experimental protocols may be, in some cases, inappropriate for detection of kinetic peculiarities. A combination of uncertainties resulting from interindividual variability, sampling, and measurement errors frequently makes it a difficult task, in practice. To decide whether a given uncommon feature is an artifact or a relevant kinetic pattern, inspection of data may not be sufficient. Additional arguments based on physiological knowledge should exist for the introduction of a time lag in a mathematical model for drug pharmacokinetics.

A present theoretical limitation should be stressed. Computer simulation is a basic requirement for investigation, analysis, fitting to data, and predictive use of the pharmacokinetic model when time lags are present in disposition kinetics. Less analytical results can be obtained in linear time-lag pharmacokinetics, as in nonlinear pharmacokinetics. While powerful numerical integration methods exist for the latter case (7), algorithms higher than first order for simulation of time-lag differential equations are not commonly available. The development of appropriate numerical methods is, therefore, a primary condition for routine use of time-lag models in pharmacokinetic analysis.

APPENDIX

Explicit Solutions of Model I and II for Initial Phase—These results are obtained through straightforward integration of models I and II on successive intervals of duration τ. In each interval, $A_1(t - \tau)$ is considered the forcing term of Eqs. 1*a* and 1*b* submitted to the appropriate initial conditions. For this reason, the complexity of the solution increases rapidly and explicit solutions are presented only for the first two τ intervals.

Model I: Single Intravenous Injection of a Dose (D)—Denoting $K_1 = k_{10} + k_{12}$ and $K_2 = k_{20} + k_{21}$ for $0 \leq t \leq \tau$:

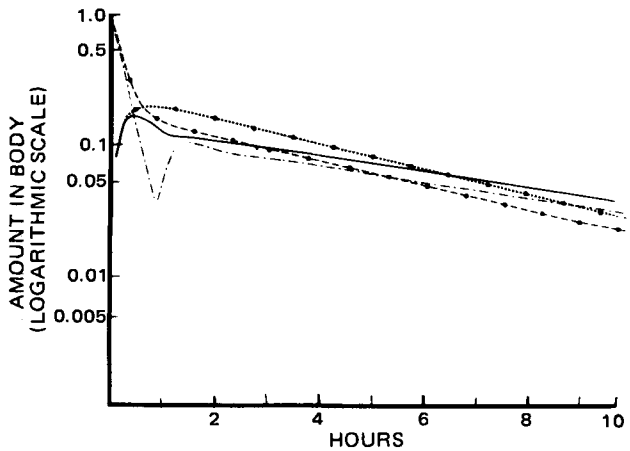

Figure 5—*Pharmacokinetic profiles after intravenous dose and oral dose. For all curves,* $k_{12} = 3.0$, $k_{10} = 1.0$, $k_{21} = 1.0$, *and* $k_{20} = 0.0\ hr^{-1}$. *Key: Without time lag* ($\tau = 0$): –●–, *intravenous; and* · ● ·, *oral. With time lag* ($\tau = 0.8\ hr$): - - -, *intravenous; and* —, *oral.*

$$A_1(t) = D\exp(-K_1 t) \quad \text{(Eq. A1}a\text{)}$$

$$A_2(t) = 0 \quad \text{(Eq. A1}b\text{)}$$

For $\tau \leq t \leq 2\tau$:

$$A_1(t) = D\exp(-K_1 t) + D\frac{k_{12}k_{21}}{K_2 - K_1}\left[\left(t - \tau - \frac{1}{K_2 - K_1}\right) \times \exp[-K_1(t-\tau)] + \frac{1}{K_2 - K_1}\exp[-K_2(t-\tau)]\right] \quad \text{(Eq. A2}a\text{)}$$

$$A_2(t) = D\frac{k_{12}}{K_2 - K_1}\left[\exp[-K_1(t-\tau)] - \exp[-K_2(t-\tau)]\right] \quad \text{(Eq. A2}b\text{)}$$

Model II: Single Oral Intake of a Dose (D)—For $0 \leq t \leq \tau$:

$$A_1(t) = D\frac{k_{21}}{K_2 - K_1}\left[\exp(-K_1 t) - \exp(-K_2 t)\right] \quad \text{(Eq. A3}a\text{)}$$

$$A_2(t) = D\exp(-K_2 t) \quad \text{(Eq. A3}b\text{)}$$

and for $\tau \leq t \leq 2\tau$:

$$A_1(t) = D\frac{k_{21}}{K_2 - K_1}[\exp(-K_1 t) - \exp(-K_2 t)] + D\frac{k_{12}(k_{21})^2}{(K_2 - K_1)^2}\left[\left(t - \tau - \frac{2}{K_2 - K_1}\right)\exp[-K_1(t-\tau)] + \left(t - \tau + \frac{2}{K_2 - K_1}\right)\exp[-K_2(t-\tau)]\right] \quad \text{(Eq. A4}a\text{)}$$

$$A_2(t) = D\exp(-K_2 t) + D\frac{k_{12}k_{21}}{K_2 - K_1}\left[\frac{1}{K_2 - K_1}\exp[-K_1(t-\tau)] - \left(t - \tau + \frac{1}{K_2 - K_1}\right)\exp[-K_2(t-\tau)]\right] \quad \text{(Eq. A4}b\text{)}$$

These expressions are especially useful to validate the numerical approximations to be used on the time interval $[0, 2\tau]$.

Approximation of the Solution of Models I and II for Large Time Values—In the range of the parameter values used in the different simulations, it has been observed that for t greater than a given time t^* which depends on the time-lag τ, the decrease of amount of drug in body is monoexponential. For $t > t^*$:

$$A_1(t) = A_1^* \exp(-\beta' t) \quad \text{(Eq. A5}a\text{)}$$

and

$$A_2(t) = A_2^* \exp(-\beta' t) \quad \text{(Eq. A5}b\text{)}$$

From Eqs. A5a and A5b are derived:

$$\ln[A_1(t)] = \ln A_1^* - \beta' t \quad \text{(Eq. A6}a\text{)}$$

$$\ln[A_2(t)] = \ln A_2^* - \beta' t \quad \text{(Eq. A6}b\text{)}$$

Division of both state equations (Eqs. 1a and 1b) by $A_1(t)$ and $A_2(t)$, respectively, leads to:

$$\frac{dA_1(t)}{A_1(t)dt} = -(k_{10} + k_{12}) + k_{21}\frac{A_2(t)}{A_1(t)} \quad \text{(Eq. A7}a\text{)}$$

$$\frac{dA_2(t)}{A_2(t)dt} = -(k_{20} + k_{21}) + k_{12}\frac{A_1(t-\tau)}{A_2(t)} \quad \text{(Eq. A7}b\text{)}$$

Equations A7a and A7b may be rewritten as:

$$\frac{d[\ln A_1(t)]}{dt} = -(k_{10} + k_{12}) + k_{21}\frac{A_2^*}{A_1^*} \quad \text{(Eq. A8}a\text{)}$$

and:

$$\frac{d[\ln A_2(t)]}{dt} = -(k_{20} + k_{21}) + k_{12}\frac{A_1^*}{A_2^*}\exp(\beta'\tau) \quad \text{(Eq. A8}b\text{)}$$

Therefore:

$$-\beta' = -(k_{10} + k_{12}) + k_{21}\frac{A_2^*}{A_1^*} \quad \text{(Eq. A9}a\text{)}$$

and:

$$-\beta' = -(k_{20} + k_{21}) + k_{12}\exp(\beta'\tau)\frac{A_1^*}{A_2^*} \quad \text{(Eq. A9}b\text{)}$$

Elimination of the ratio A_2^*/A_1^* from Eqs. A9a and A9b leads to the algebraic equation to be solved for β':

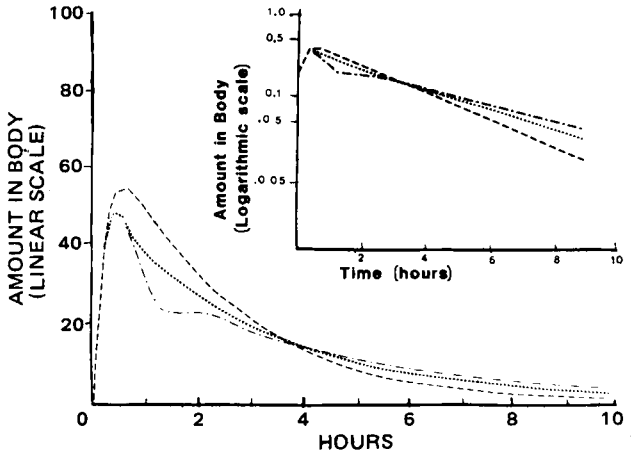

Figure 6—*Effect of time lag on pharmacokinetic profile after oral intake of the drug. For all curves,* $k_{12} = 1.0$, $k_{10} = 0.5$, $k_{21} = 3.0$, *and* $k_{20} = 0.2\ hr^{-1}$. *Key: ---,* $\tau = 0$ *hr; . . .,* $\tau = 0.5$ *hr; and -·-,* $\tau = 1.0$ *hr.*

$$(\beta')^2 - \beta'(k_{12} + k_{10} + k_{21} + k_{20}) + (k_{12} + k_{10})(k_{21} + k_{20}) - k_{12}k_{21}\exp(\beta'\tau) = 0 \quad \text{(Eq. A10)}$$

With $K_1 = k_{10} + k_{12}$ and $K_2 = k_{20} + k_{21}$, Eq. A10 can be rewritten as:

$$f(\beta') \triangleq (\beta' - K_1)(\beta' - K_2) - k_{12}k_{21}\exp(\beta'\tau) = 0 \quad \text{(Eq. A11)}$$

Function f is positive for $\beta' = 0$ and negative for $\beta' = K_1$ and $\beta' = K_2$. Furthermore, its derivative is negative for β' less than the minimum of K_1 and K_2. So f has one unique root on [0, min (K_1, K_2)]. This is the smallest root for β' and the relevant one for large time values.

Sensitivity Analysis of β'—*Sensitivity* versus *the Time Lag* (τ)—Assuming all microconstants to be kept at a fixed value, the partial derivative of β' with respect to τ is deduced from the differentiation of f. Hence:

$$(2\beta' - K_1 - K_2)\frac{\partial\beta'}{\partial\tau} - k_{12}k_{21}\exp(\beta'\tau)\left(\tau\frac{\partial\beta'}{\partial\tau} + \beta'\right) = 0 \quad \text{(Eq. A12).}$$

and:

$$\frac{\partial\beta'}{\partial\tau}[2\beta' - K_1 - K_2 - k_{12}k_{21}\tau\exp(\beta'\tau)] = \beta' k_{12}k_{21}\exp(\beta'\tau) \quad \text{(Eq. A13)}$$

If $\beta' < K_1$ and $\beta' < K_2$, the coefficient of $\partial\beta'/\partial\tau$ is negative. Furthermore, the second member of (Eq. A13) is positive. Therefore:

$$\frac{\partial\beta'}{\partial\tau} < 0 \quad \text{(Eq. A14)}$$

For any value of the microconstants, β' decreases when τ increases and vice versa. Accordingly, the half-life increases when the time lag is enhanced, regardless of the combination of microconstants.

Sensitivity versus *the Transfer Rate Constants* k_{12} *and* k_{21}—When partial differentiation of β' with respect to k_{12} is considered, an equation similar to Eq. A13 is obtained. In the present case, the second member is equal to $\beta' - K_2 + k_{21}\exp(\beta'\tau)$. The sign of $\partial\beta'/\partial k_{12}$ is the opposite sign of the previous expression. In abbreviated form:

$$\text{sign}(\partial\beta'/\partial k_{12}) = -\text{sign}[\beta' - K_2 + k_{21}\exp(\beta'\tau)] \quad \text{(Eq. A15)}$$

After replacement of $k_{21}\exp(\beta'\tau)$ according to Eq. A11, multiplication by k_{12} (positive) and division by $(\beta' - K_2)$ (negative), it follows that:

$$\text{sign}\left(\frac{\partial\beta'}{\partial k_{12}}\right) = \text{sign}(\beta' - k_{10}) \quad \text{(Eq. A16)}$$

According to the definition of function f (Eq. A11) and to its properties on the interval [0, min (K_1, K_2)], the sign of $(\beta' - k_{10})$ verifies:

$$\beta' - k_{10} > 0 \Leftrightarrow f(k_{10}) > 0 \quad \text{(Eq. A17}a\text{)}$$

$$\beta' - k_{10} < 0 \Leftrightarrow f(k_{10}) < 0 \quad \text{(Eq. A17}b\text{)}$$

As:

$$f(k_{10}) = k_{12}k_{21}[1 - \exp(k_{10}\tau)] + k_{12}(k_{20} - k_{10}) \quad \text{(Eq. A18)}$$

We get the following results for $\partial\beta'/\partial k_{12}$:

$$\frac{\partial\beta'}{\partial k_{12}} < 0 \text{ if } k_{20} < k_{10} + \Delta_1 \quad \text{(Eq. A19a)}$$

$$\frac{\partial\beta'}{\partial k_{12}} = 0 \text{ if } k_{20} = k_{10} + \Delta_1 \quad \text{(Eq. A19b)}$$

$$\frac{\partial\beta'}{\partial k_{12}} > 0 \text{ if } k_{20} > k_{10} + \Delta_1 \quad \text{(Eq. A19c)}$$

where $\Delta_1 = k_{21}[\exp(k_{10}\,\tau) - 1]$.

Note that the test condition does not depend on k_{12} itself. Sensitivity analysis of β' *versus* k_{21} relies on similar algebraic manipulations. Therefore:

$$\frac{\partial\beta'}{\partial k_{21}} < 0 \text{ if } k_{10} < k_{20} + \Delta_2 \quad \text{(Eq. A20a)}$$

$$\frac{\partial\beta'}{\partial k_{21}} = 0 \text{ if } k_{10} = k_{20} + \Delta_2 \quad \text{(Eq. A20b)}$$

$$\frac{\partial\beta'}{\partial k_{21}} > 0 \text{ if } k_{10} > k_{20} + \Delta_2 \quad \text{(Eq. A20c)}$$

where $\Delta_2 = k_{12}[\exp(k_{20}\tau) - 1]$.

Clear-cut results can be given in some cases. If $k_{20} < k_{10}$, $\partial\beta'/\partial k_{12}$ is always negative and if $k_{20} > k_{10}$, the same is true for $\partial\beta'/\partial k_{21}$, regardless of the combination of other parameters. For other cases, the test condition should be computed and applied.

Sensitivity versus *the Elimination Rate Constants* k_{10} *and* k_{20}—Differentiation of f with respect to β' and k_{10} leads to:

$$\frac{\partial\beta'}{\partial k_{10}}[2\beta' - K_1 - K_2 - k_{12}k_{21}\,\tau\exp(\beta'\tau)] = \beta' - K_2 \quad \text{(Eq. A21)}$$

As β' is less than K_2, the second member is negative in the present case. Hence:

$$\frac{\partial\beta'}{\partial k_{10}} > 0 \quad \text{(Eq. A22)}$$

Similarly it can be shown that:

$$\frac{\partial\beta'}{\partial k_{20}} > 0 \quad \text{(Eq. A23)}$$

Therefore, an increase in elimination processes, through either k_{10} or k_{20} will always increase β' and shorten the half-life $T^{\beta'}_{1/2}$.

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Combined Water-Soluble Carriers for Coprecipitates of Tolbutamide

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Abstract □ A study was conducted on the influence of single and combined carriers on the dissolution rate of tolbutamide from its coprecipitates. All of the water-soluble carriers investigated enhanced the dissolution rate of tolbutamide, but the combination of 40% polyethylene glycol 6000–60% dextrose as the carrier for a 1:1 coprecipitate yielded the most rapid dissolution of tolbutamide. Other carriers used were polyethylene glycol 6000, polyethylene glycol 4000, dextrose, and mannitol, alone or combined in various proportions.

Keyphrases □ Tolbutamide—coprecipitates, combined water-soluble carriers, dissolution □ Solubility—combined water-soluble carriers for coprecipitates of tolbutamide, dissolution □ Dissolution—effect of combined water-soluble carriers, coprecipitates of tolbutamide

The rate at which a drug dissolves from its intact or disintegrated and deaggregated form in the GI tract is often responsible for the rate at which the drug appears in the blood, *i.e.*, the absorption rate of the drug. When this is the case, dissolution is said to be the rate-limiting process.

BACKGROUND

The sulfonylurea compounds employed as oral hypoglycemic compounds are considered to be poorly water soluble. Variation in the dissolution rates of these compounds has been reported (1). The influence of *in vitro* dissolution rates on the rate of decline of blood sugar levels has also been studied (2). Varley (3) investigated two formulations of tolbutamide, both generically equivalent in terms of chemical content and USP specifications; he found they were not equivalent as measured by availability of drug to the patient (serum drug levels) or on the basis of therapeutic efficacy (hypoglycemic response). Levy (4) found marked variation in the dissolution rates of two brands of tolbutamide tablets and recommended that patients should not change the brand of the drug they were taking unless the dose of the new brand was established. Another report (5) showed a correlation between percentage of the tolbutamide dose excreted in the urine as its metabolite and the surface area of tolbutamide in the dosage form.

The influence of povidone and polyethylene glycol 6000 on the dissolution rate of tolbutamide was studied (6). It was found that both carriers favorably increased the dissolution rate of the drug and that a complex formed between the drug and povidone but not between tolbutamide and polyethylene glycol. Later it was found (7) that the solid dispersion of

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