Some Considerations as to the Determination and Significance of Biologic Half-Life

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Abstract □ The biologic half-life of a drug as determined from the terminal exponential phase of appropriate semilogarithmic plots is shown to dictate the steady-state levels of drug upon repetitive dosing, regardless of how low the plasma concentrations are or how little drug remains in the body, after a single dose, before the terminal exponential phase occurs. Accordingly, premature termination of pharmacokinetic studies may yield erroneous underestimates of half-life and, in turn, poor predictions of steady-state levels. Since the plasma levels of a drug after administration of a single dose may be so low upon attainment of the terminal exponential phase that they are not detected by presently available analytical methods, the true biologic half-life of certain drugs may be indeterminable from single-dose studies. The possible lack of attainment of the terminal exponential phase is also of concern in repetitive dosing pharmacokinetic studies where the half-life is determined after each dose. Under these conditions, not only may the true half-life be underestimated but the artifactual, apparent half-life may increase with increasing dose, erroneously suggesting self-inhibition of biotransformation processes or capacity-limited elimination.

Keyphrases □ Biologic half-life—theoretical considerations of determination, significance □ Computer-simulated data—determination, significance of biologic half-life □ Half-life, drug biologic—theoretical considerations for correct interpretation

Biologic half-life is probably the most critical pharmacokinetic parameter of a drug, since it markedly influences the duration of drug action as well as the degree of accumulation of the drug in the body upon repetitive dosing. Knowledge of the half-life of a drug can be extremely useful in a predictive sense, particularly with respect to the design of rational dosing regimens. However, since access to compartments in the biologic system and frequency of sampling are usually limited, experimental design is a critical consideration in pharmacokinetic studies, and even the determination of biologic half-life of a drug may pose considerable problems. Wagner (1) discussed several possible errors in the plotting and interpretation of semilogarithmic plots of blood level and urinary excretion data that may lead to gross inaccuracies in the estimation of half-life. In addition, the lack of a specific assay for a drug in the plasma or urine and the reliance upon levels of total radioactivity may yield a biased estimate of half-life (2, 3).

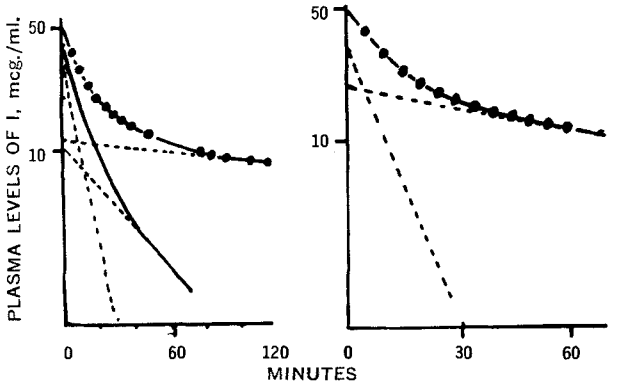
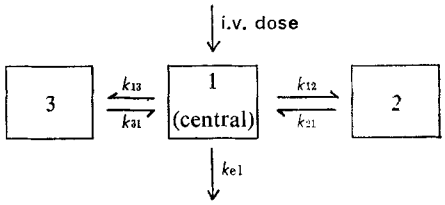


Figure 1—*Plasma levels of I in the dog after a single injection (20 mg./kg. i.v.) during a 1-hr. and 2-hr. experiment. Based on Figs. 1 and 2 in* Reference 4.



Scheme I—*Three-compartment open model proposed to describe the time course of I in the dog. According to Loo* et al. *(4),* $k_{12} = 2.28\ hr.^{-1}$, $k_{21} = 3.60\ hr.^{-1}$, $k_{13} = 1.50\ hr.^{-1}$, $k_{31} = 0.84\ hr.^{-1}$, *and* $k_{el} = 0.72\ hr.^{-1}$.

Another problem, which has received little attention to date, is the application of inappropriate mathematical models to blood level or urinary excretion data because of the limited duration of the sampling period. Pharmacokinetic studies may be terminated too early for several reasons. An arbitrary experimental protocol may call for blood sampling over a fixed period without considering the pharmacokinetic properties of the drug. Moreover, analytical methods may not be sufficiently sensitive, so that low but persistent levels of drug are not detected.

Under these conditions, significant underestimates of half-life may be obtained if two-compartment kinetics are erroneously treated as single-compartment kinetics or if a three-compartment model is interpreted in terms of the two-compartment model. An example of the latter situation is shown in Fig. 1. According to Loo *et al.* (4), the plasma levels of 5-(dimethyltriazeno)-imidazole-4-carboxamide (I), a cancer chemotherapeutic agent, over a 2-hr. period after intravenous administration of 20 mg./kg. in a dog can be described in terms of a three-compartment open model. Plasma concentrations (C_p) as a function of time (in minutes) are given by $C_p = 30.5 \exp(-0.117t) + 10.3 \exp(-0.028t) + 11.4 \exp(-0.003t)$, yielding a half-life of 231 min. for the terminal exponential phase (β-phase). However, if the determination of plasma level is halted 1 hr. after administration, a markedly different and incorrect pharmacokinetic profile emerges. In this case, plasma concentrations as a function of time (in minutes) are given by $C_p = 32.7 \exp(-0.111t) + 19.2 \exp(-0.008t)$, yielding a half-life of 87 min. for the apparent terminal exponential phase, which represents a threefold error.

The present report concerns the consequences of this type of error with respect to the prediction of drug accumulation and steady-state blood levels upon multi-

Table I—Nonlinear Least-Squares Regression Analysis of Simulated Central Compartment Levels of I after Several Doses of 100 mg. at Hourly Intervals According to the Equation: Levels = $A \exp(-\alpha)t + B \exp(-\beta)t$

Dose	Sum of Squared Deviations	A[a], mg.	α[a], hr.$^{-1}$	B[a], mg.	β[a], hr.$^{-1}$	$(t_{1/2})\beta$, hr.
1	0.024	63.91 (0.25)	6.418 (0.071)	34.92 (0.33)	0.479 (0.011)	1.45
2	0.035	65.42 (0.30)	6.273 (0.082)	54.95 (0.39)	0.387 (0.008)	1.79
4	0.041	65.94 (0.31)	6.217 (0.086)	82.71 (0.40)	0.314 (0.005)	2.21
8	0.043	66.09 (0.32)	6.200 (0.086)	115.00 (0.40)	0.274 (0.004)	2.53
12	0.044	66.12 (0.32)	6.194 (0.087)	130.58 (0.40)	0.262 (0.003)	2.65
16	0.044	66.14 (0.32)	6.193 (0.087)	138.10 (0.40)	0.257 (0.003)	2.70

[a] Parenthetic values beneath each parameter estimate denote the standard error of the estimate.

ple dosing as well as with respect to the determination of apparent half-lives during repetitive dosing.

METHOD

The pharmacokinetics of distribution and elimination of I in the dog were assumed to follow the three-compartment open model (Scheme I) suggested by Loo *et al.* (4). Simulated "body" and compartment levels as a function of time after initial and repetitive intravenous administration of I were obtained by using the appropriate differential equations and rate constants as input data for the "MIMED" digital computer analog-simulation program (5). These simulated levels were given equal weight and were used as input data for the digital computer program of Marquardt (6) to obtain nonlinear least-squares regression fits to the data.

RESULTS

Steady-State Blood Levels in Multicompartment Models—According to Wagner *et al.* (7), the average blood (serum) or plasma concentration of drug ($\bar{C}$) at steady state after multiple dosing is given by:

$$\bar{C} = F \cdot D/V \cdot K \cdot \tau \qquad \text{(Eq. 1)}$$

where D is the dose given at the beginning of each dose interval, F is the fraction of each dose absorbed, τ is the length (in units of time) of the dosage interval, and V is the apparent volume of distribution of the drug. According to Wagner *et al.* (7), K is the "first-order rate constant for overall loss of drug from the blood." It is also implicit in the work of a number of authors that the total area under the plasma concentration *versus* time curve (AUC) after a single dose is given by:

$$\text{AUC} = \int_0^\infty C(t)dt = F \cdot D/V \cdot K \qquad \text{(Eq. 2)}$$

Hence,

$$\bar{C} = \int_0^\infty C(t)dt/\tau \qquad \text{(Eq. 3)}$$

While it is clear that Eqs. 1 and 3 can be readily applied to a one-compartment model, some questions are raised as to how to apply these very useful relationships to multicompartment models. The major question relates to the meaning of K and V in the multicompartment model. A resolution of the problem is apparent based on the relationships developed by Gibaldi *et al.* (8). These workers showed that in a two-compartment model:

$$\int_0^\infty C(t)dt = F \cdot D/V \cdot \beta \qquad \text{(Eq. 4}$$

where V is an apparent volume of distribution[1], and β is 2.303 times the slope of the terminal exponential phase of the semilogarithmic plot of plasma concentration or amount of drug in the body *versus* time. It is implicit in Eqs. 22*a* and 23*a* of *Reference 8* that Eq. 4 is valid for any multicompartment model. The required assumptions are that elimination occurs from the central compartment and that the term β is related to the terminal exponential phase of the semilogarithmic plot of plasma or body level of drug *versus* time, regardless of the number of exponential phases that precedes the terminal phase. This relationship was also derived somewhat differently and independently by Westlake (9). Therefore,

$$\bar{C} = (F \cdot D)/V \cdot \beta \cdot \tau = (F \cdot D)\, t_{1/2}/0.693V \cdot \tau \qquad \text{(Eq. 5)}$$

where V is equivalent to $(V_d)_{\text{area}}$ or $(V_d)_\beta$ (8).

According to Eq. 5, it is clear that in the multicompartment situation, the plasma levels of drug or the amount of drug in the body, in the steady-state after multiple dosing, are related to the half-life of the drug as determined from the terminal exponential phase of the appropriate semilogarithmic plots. This half-life dictates the steady-state conditions, regardless of how low the plasma concentrations are or how little drug remains in the body after a single dose, before the terminal exponential phase occurs.

Hence, the type of error in the estimation of half-life discussed by Loo *et al.* (4) can have a profound effect on the prediction of steady-state levels. This is readily apparent if the erroneous β obtained from the plasma levels of I during the 1-hr. period after intravenous administration is used to predict steady-state levels of I upon repetitive dosing of 100 mg. every hour. Use of this incorrect estimate yields a prediction of $(\bar{C} \cdot V)$ equal to 208 mg. This is considerably lower than a $(\bar{C} \cdot V)$ value of 555 mg. predicted by using the β-value obtained from the plasma levels of I during the 2-hr. period after intravenous administration.

Since plasma levels of a drug after administration of a single dose may be so low upon attainment of the true β-phase that they are not detected by presently available analytical methods, it follows that the true biologic half-life of a drug, *i.e.*, $0.693/\beta$, may be indeterminable from single-dose pharmacokinetic studies. Hence, the authors suggest that the half-life of certain drugs be estimated from steady-state studies using Eq. 5.

Determination of Half-Life during Repetitive Dosing—An apparent advantage in repetitive dosing pharmacokinetic studies is that the half-life may be determined after each dose. Presumably, drug-related enzyme induction or inhibition, or capacity-limited biotransformation, may be revealed by monitoring the half-life as a function of the number of doses or the degree of drug accumulation. This approach, however, can artifactually produce apparent changes in half-life which have no relationship to changes in drug elimination. Obviously, during the course of a rational repetitive dosing study, the subsequent dose is administered long before the blood

[1] As discussed in *Reference 8*, V is actually a proportionality constant, with units of volume, which relates the plasma concentration of drug to the amount of drug in the body, once pseudodistribution equilibrium is attained.

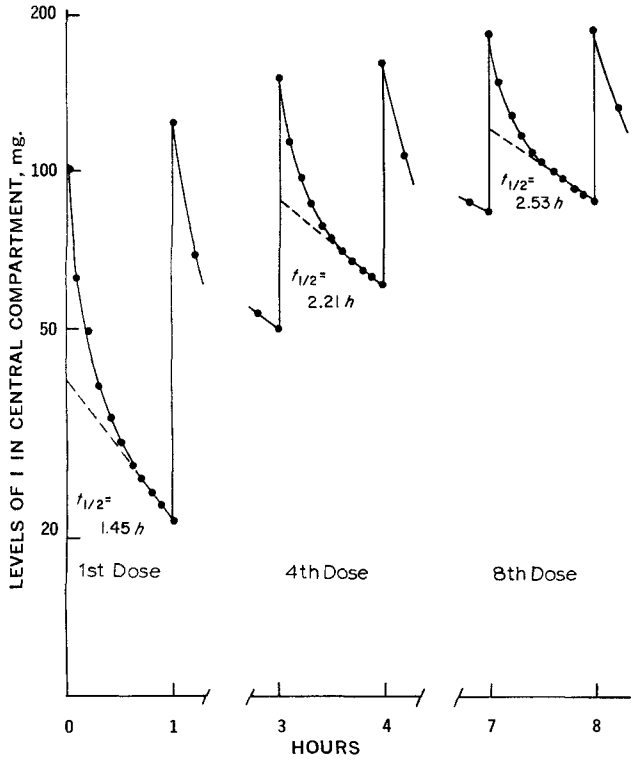


Figure 2—*Simulation of central compartment levels of I in the dog upon repetitive dosing of 100 mg. at hourly intervals employing the three-compartment open model shown in Scheme I. Interpretation of the curves according to a two-compartment model suggests erroneously that the half-life increases upon multiple dosing.*

levels of drug from the previous dose have run their time course and diminished to zero. Hence, determination of half-life during repetitive dosing may be based on blood levels that do not represent the terminal exponential (β) phase.

This artifact in itself can introduce serious error, but the repetitive dosing situation is still more complicated. During the course of dosing, the pharmacokinetically distinguishable body compartments that are in equilibrium with the central (plasma-containing) compartment contain more and more drug at the end of each dosing interval, and the levels asymptotically approach steady-state conditions. Hence, with each subsequent dose, a smaller and smaller fraction of the total amount of drug present must leave the central compartment and enter a peripheral compartment to achieve distribution equilibrium which signals the initiation of monoexponential loss of drug from the body (*i.e.*, the β-phase). This fraction becomes constant once steady state is achieved. Therefore, more and more of the true pharmacokinetic profile of a drug may be revealed during a given dosing interval as steady state is approached.

A possible consequence of this interesting distribution phenomenon is that a two-compartment model may be needed to describe plasma levels of the drug after the *n*th dose, while a one-compartment model is all that is *apparently* needed to describe plasma levels of the drug after the first dose. On the other hand, the net fraction of the drug distributed from the central compartment to a peripheral compartment may be so small at steady state that the existence of the compartment may not be apparent, whereas its existence is quite apparent after a single dose. However, given the limited data, particularly in human studies, a more likely consequence of this distribution phenomenon is that the apparent half-life of the drug will be assumed to increase upon repetitive dosing or upon elevating the body levels of drug.

To exemplify this situation, computer simulations were obtained of levels of I in the dog upon repetitive dosing. Figure 2 shows the central compartment levels of drug after intravenous administration of the first, fourth, and eighth doses. The time course of these curves are identical to the time course of plasma concentration curves. The simulated data after each dose were then subjected to nonlinear least-squares regression analysis. In agreement with Loo *et al.* (4), the data in each case were well described in terms of the two-compartment model, despite the fact that they were generated according to a three-compartment model. The appropriate pharmacokinetic and statistical parameters resulting from the curve fitting after each dose are summarized in Table I. It is evident from inspection of these data as well as from Fig. 2 that if the drug levels in the central compartment after each dose are interpreted in terms of the two-compartment model, then the apparent half-life increases upon repetitive dosing. Although application of the two-compartment model to these data is in error, such application is certainly reasonable from a statistical point of view (Table I).

Interestingly, Doluisio and Dittert (10) reported that the apparent half-life of several tetracyclines increased upon repetitive dosing. These workers found that the half-lives of tetracycline, demethylchlortetracycline, methacycline, and doxycycline increased from 6.3, 11.0, 7.0, and 8.3 hr., respectively, after a single dose to 10.8, 13.6, 14.3, and 16.6 hr., respectively, during multiple (4-day) administration of therapeutic doses every 12 hr. Van Rossum (11) recently suggested that these data should be interpreted in terms of a two-compartment model rather than the one-compartment model used by Doluisio and Dittert (10). Hence, although cursory examination of the data might suggest self-inhibition or capacity-limited elimination of tetracycline, it is more likely that the apparent changes in half-life upon repetitive dosing are due to the distribution phenomenon and mathematical artifacts already discussed.

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