Estimating the Accumulation of Drugs

Keyphrases □ Drug accumulation—estimation during chronic dosing, theoretical *versus* empirical calculations □ Accumulation ratios—impact of lag time, effect of dosing

To the Editor:

Several methods are available to estimate the accumulation (R) of drugs during chronic dosing. The following equations are the ones most commonly used:

$$R_1 = \frac{AUC^1_{0-\infty}}{AUC^1_{0-\tau}} = \frac{AUC^{ss}_{0-\tau}}{AUC^1_{0-\tau}} \quad \text{(Eq. 1)}$$

$$R_2 = \frac{C_{min(ss)}}{C_{min(1)}} \quad \text{(Eq. 2)}$$

$$R_3 = 1/1 - e^{-\beta\tau} \quad \text{(Eq. 3)}$$

where $AUC^1_{0-\tau}$ and $AUC^1_{0-\infty}$ are the areas under the plasma concentration–time curves during a dosing interval and from time 0 to ∞ following a single dose, and $AUC^{ss}_{0-\tau}$ is the area under the plasma concentration–time curves during a dosing interval at steady state. $C_{min(1)}$ and $C_{min(ss)}$ are the plasma concentrations immediately prior to the administration of the second dose and any dose at steady state, respectively; and β and τ are the elimination rate constant and dosing interval, respectively.

Equations 1 and 2 can be determined empirically, whereas equation 3 is a theoretical calculation. If the pharmacological effect of the drug is a function of the plasma concentration, the R_1 values reflect the relevant accumulation, in that R_1 is a simple ratio of the observed concentrations during a dosing interval after a dose at steady state divided by the observed concentrations during the dosing interval after the first dose. R_2 values would be expected to closely approximate the relevant accumulation ratio (R_1) when k_a is larger compared with β but diverge as k_a approaches β, since the time of the maximum plasma concentration (C_{max}) moves closer to the time of drug administration during multiple dosing (1), and this will result in differences in C_{min} during multiple dosing. In general, the equation that uses β as the sole determinant of R (R_3) would be expected to deviate the most from R_1 and, in fact, only truly represents the accumulation during intravenous bolus administration.

Accumulation ratios (R) were estimated with a dosing interval equal to the half-life under known conditions using each of these equations with and without a lag time (t_{lag}) prior to the onset of absorption. The results of these calculations are presented in Table I. R_1 is always larger than R_2 and R_3. As the absorption half-life increases and k_a/β decreases these differences become more pronounced. In addition, when a lag time is incorporated the deviations among the three methods become more obvious. The reason for this deviation due to a lag time is displayed graphically in Fig. 1. Following the first dose, the lag time reduces the area during a dosing interval, whereas at steady state the lag time does not affect the area during a dosing interval.

Table I—Accumulation Ratios (R) Estimated by Various Commonly Used Methods with a Dosing Interval of 24 hr [a]

Parameter	k_a/β 24		12		4		2		1.1	
t_{lag}, hr	0	2	0	2	0	2	0	2	0	2
R_1	2.1	2.2	2.2	2.4	2.8	3.1	4.0	4.5	6.1	6.9
R_2	2.0	2.0	2.0	2.0	2.1	2.2	2.7	2.8	3.7	4.0
R_3	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0

[a] $t_{1/2}\,k_a$ = 1, 2, 6, 12, and 21.8 hr; $t_{1/2}\,\beta$ = 24 hr; τ = 24 hr.

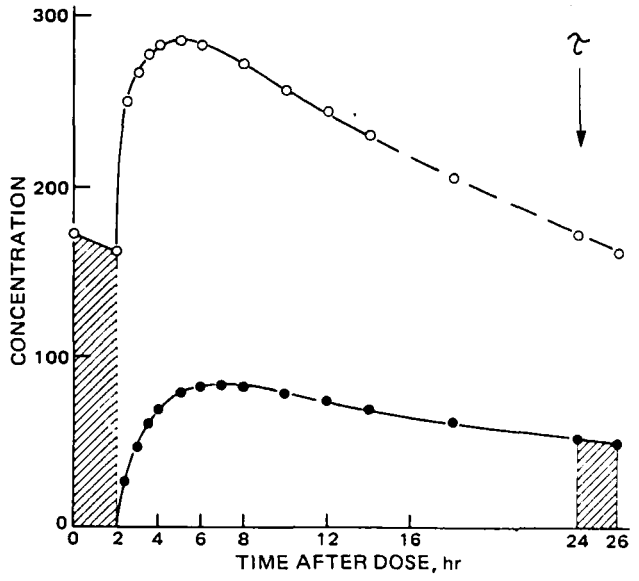

Figure 1—*Concentration–time profiles during a 24-hr dosing interval following first (—) and steady-state (- - -) doses when an absorption lag time occurs. The area that affects the prediction of accumulation is shaded. No area is lost at steady state, whereas the AUC from 24 to 26 hr is lost after a single dose.*

R values simulated when the same k_a/β ratios are employed but the dosing interval (τ) is altered are presented in Table II. It is apparent that the dosing interval significantly influences the deviations from R_1. Shorter dosing intervals cause greater deviations from the relevant accumulation ratio (R_1).

A composite view shows that several factors including lag time, dosing interval, and the ratio of k_a/β can influence the predictive capacity of Eqs. 2 and 3 compared with the true accumulation ratio estimated by Eq. 1. Although the need to use Eqs. 2 and 3 with caution and under specific conditions has been recognized (2), the impact of lag time and the actual deviations observed under appropriate use has been generally overlooked (3, 4). When one doses every

Table II—Accumulation Ratios (R) Estimated by Various Commonly Used Methods with a Dosing Interval of 12 or 48 hr [a]

Parameter	k_a/β 24		12		4		2		1.1	
τ, hr	12	48	12	48	12	48	12	48	12	48
R_1	3.8	1.4	4.3	1.4	7.1	1.5	11.6	1.8	19.8	2.4
R_2	3.4	1.3	3.5	1.3	4.6	1.3	6.8	1.4	10.8	1.7
R_3	3.4	1.3	3.4	1.3	3.4	1.3	3.4	1.3	3.4	1.3

[a] $t_{1/2}\,k_a$ = 1, 3, 6, 12, and 21.8 hr; $t_{1/2}\beta$ = 24 hr.

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half-life, as is generally accepted as optimum therapy from a pharmacokinetic point of view, deviations occur even when k_a/β is large. When the dosing interval is decreased the deviations become greater. When k_a/β approached unity, as would be expected from certain controlled-release dosage forms, the deviations become enormous. In addition, it must be realized that although R_2 more closely reflects R_1 values than does R_3, it is not a predictive method, in that one must achieve steady state to determine $C_{min(ss)}$, whereas R_1 and R_3 can be used predictively following a single dose. These variables must be kept in mind when one is attempting to anticipate or predict drug accumulation and consequent pharmacological effects from single-dose data.

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Fraction Unbound in Interstitial Fluid

Keyphrases □ Pharmacokinetics—fraction unbound in interstitial fluid, relationship between binding in interstitial and vascular space

To the Editor:

The influence of protein binding of drugs on their pharmacological effect and pharmacokinetic disposition has been widely studied (1–3). However, most of the experimental observations have involved the interaction of drugs with plasma or serum proteins and not extravascular proteins. The lack of useful, experimental observations in this area is a result of the difficulty in obtaining representative tissue samples and the inadequate methods for performing tissue-binding studies (4). A mathematical approach has been derived (5) for estimating the fraction unbound in the "tissue" space utilizing a calculated volume of distribution term and anticipating physiological spaces. However, this approach is limited and only provides a complex average fraction unbound located outside the vascular space. Therefore, alternative theoretical approaches, as well as experimental methods need to be developed.

Nowhere is the role of plasma and tissue binding of greater interest than in the area of antibiotic therapy (6, 7). In general, β-lactam antibiotics are restricted in their distribution to the vascular space and the interstitial fluids; they do not penetrate intracellularly. Attempts to study the tissue (interstitial) binding of these antibiotics have centered on the collection of fluid from tissue cages (8), but the physiological character of the collected fluid has been questioned (9). The purpose of the present communication is to derive a theoretical relationship that relates the binding of a drug in the extravascular–extracellular or interstitial space to the binding in the vascular space. The original model on which this work is based was put forth by Øie *et al.* (10) and was recently used to describe the distribution of ceftriaxone (11). This theoretical relationship is used to explain the lack of distributional changes occurring with ceftriaxone despite the dramatic changes in the fraction unbound in the plasma (11).

The interaction of drugs with plasma proteins is usually described by the following Langmuir binding isotherm:

$$C_{BP} = \sum_{i=1}^{m} \frac{n_i P^* C_U}{Kd_i + C_U} \qquad \text{(Eq. 1)}$$

where C_{BP} is the plasma concentration of bound drug, m is the number of classes in binding sites, n_i is the number of binding sites for the ith class of binding sites, P is the concentration of the binding protein located in the vascular space, C_U is the concentration of unbound drug, and Kd_i is the equilibrium dissociation constant for the ith class of binding sites.

The presence of plasma proteins (*i.e.*, albumin) in the interstitial fluids has been well documented (12). If one assumes that the drug–protein interaction in the interstitial space is identical to the interaction in the vascular space (equivalent capacity and affinity constants), then a similar Langmuir relationship can be written for the interstitial binding:

$$C_{BE} = \sum_{i=1}^{m} \frac{n_i E^* C_U}{Kd_i + C_U} \qquad \text{(Eq. 2)}$$

where C_{BE} is the interstitial concentration of the bound drug and E is the concentration of binding protein in the interstitial space.

Equation 1 can be rewritten to factor out the protein and unbound concentration to yield:

$$C_{BP} = P^* C_U^* \sum_{i=1}^{m} \frac{n_i}{Kd_i + C_U} \qquad \text{(Eq. 3)}$$

For ease of manipulation, let a new parameter, S, replace the summation term:

$$C_{BP} = P^* C_U^* S \qquad \text{(Eq. 4)}$$

Given the assumptions concerning equivalent binding proteins in the vascular and interstitial spaces, and the additional assumptions of: (*a*) equal unbound drug concentration in both physiological spaces; (*b*) Kd_i does not change at lower protein concentrations; (*c*) other mechanisms of tissue distribution such as active transport, selective membrane permeability, and ion trapping are not present, then the S term for both C_{BP} and C_{BE} are equal, and a similar rearrangement and substitution can be written for C_{BE}:

$$C_{BE} = E^* C_U^* S \qquad \text{(Eq. 5)}$$

By definition, the fraction unbound in the plasma or vascular space (f_P) may be written as:

$$f_P = \frac{C_U}{C_U + C_{BP}} = \frac{1}{1 + P^* S} \qquad \text{(Eq. 6)}$$

A similar fraction unbound in the interstitial space (f_E) may be written as:

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