erence for either enantiomer. This result is in agreement with results obtained previously with human cell cultures and each pure enantiomer as well as the racemic mixture. No significant difference in the cytotoxic effects or the relative abilities to prevent an increase in cell numbers was observed with the three forms (16).

Control runs with plasma blanks showed no interferences with either the I or fluorouracil procedure. The accuracy and the concentration range over which both methods were tested are indicated in Table I. The correlation coefficients for the amount added *versus* the amount calculated in Table I are 0.999 for both sets of data, indicating that both analyses are linear in the concentration ranges tested. The methods as outlined permit the detection of 0.25 μg of I and 0.025 μg of fluorouracil/ml of plasma and are specific for the intact molecules. The sensitivity and applicability of these analyses indicate that they are suitable for these types of studies, and clinical investigations utilizing these procedures are currently being performed.

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[17] *Note added in proof:* Similar methods for the concurrent determination of I and fluorouracil were reported recently by A. T. Wu, H. J. Schwandt, and W. Sadee, *Res. Commun. Chem. Pathol. Pharmacol.* **14**, 89 (1976).

Estimation of Pharmacokinetic Parameters from Postinfusion Blood Level Data Obtained after Simultaneous Administration of Intravenous Priming and Infusion Doses

SAMPAT M. SINGHVI

Abstract □ Occasionally, it is desirable to attain steady-state blood drug levels rapidly in pharmacokinetic studies as well as in the treatment of certain diseases. In these cases, it is useful to administer an intravenous priming dose in combination with continuous drug infusion. Mathematical relationships are presented for the determination of pharmacokinetic parameters in these situations using postinfusion blood drug level data. The parameters obtained by this method are identical to the parameters obtained after a rapid intravenous injection of a drug.

Keyphrases □ Pharmacokinetic parameters—determined from postinfusion blood level data after simultaneous intravenous priming and infusion doses □ Dosage regimens—simultaneous intravenous priming and infusion doses, pharmacokinetic parameters determined from postinfusion blood level data

Methods for the assessment of pharmacokinetic parameters from postinfusion blood level data obtained after continuous intravenous infusion were presented previously (1). However, in practice, a rapid intravenous priming dose is often given simultaneously with the beginning of a continuous infusion to achieve steady-state blood drug levels rapidly in the body. This paper presents the treatment of postinfusion blood concentration data for the estimation of pharmacokinetic parameters in those instances.

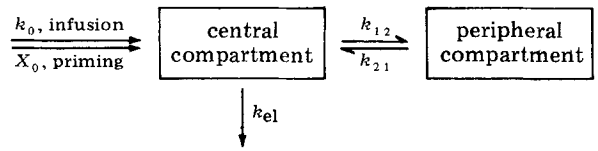
THEORY AND DISCUSSION

Two-Compartment Model—For a drug that exhibits the characteristics of a two-compartment open model (Scheme I), the decay of blood concentration, $C_{p(\text{bolus})}$, with time t, after a rapid intravenous injection (assuming first-order elimination and distribution kinetics) can be expressed as (2):

$$C_{p(\text{bolus})} = \frac{X_0(\alpha - k_{21})}{V_c(\alpha - \beta)} e^{-\alpha t} + \frac{X_0(k_{21} - \beta)}{V_c(\alpha - \beta)} e^{-\beta t} \qquad \text{(Eq. 1)}$$

If:

$$A = \frac{X_0(\alpha - k_{21})}{V_c(\alpha - \beta)} \qquad \text{(Eq. 2)}$$



Scheme I

and:

$$B = \frac{X_0(k_{21} - \beta)}{V_c(\alpha - \beta)} \quad \text{(Eq. 3)}$$

then:

$$C_{p(\text{bolus})} = Ae^{-\alpha t} + Be^{-\beta t} \quad \text{(Eq. 4)}$$

where A and B are intercepts at zero time, α and β are disposition rate constants, k_{12} and k_{21} are distribution rate constants, k_{el} is the first-order elimination rate constant from the central compartment, X_0 is the intravenous priming dose, and V_c is the volume of the central compartment.

Similarly, when a drug is administered as a continuous infusion at a constant rate, k_0, the blood levels, $C_{p(\text{inf})}$, at any time t during and after cessation of infusion can be described as (2):

$$C_{p(\text{inf})} = \frac{k_0(k_{21} - \alpha)(1 - e^{\alpha T})}{V_c\alpha(\alpha - \beta)} e^{-\alpha t} + \frac{k_0(\beta - k_{21})(1 - e^{\beta T})}{V_c\beta(\alpha - \beta)} e^{-\beta t} \quad \text{(Eq. 5)}$$

where T is the duration of infusion. The blood drug level after cessation of infusion also can be expressed as:

$$C_{p(\text{inf})} = \frac{k_0(k_{21} - \alpha)(1 - e^{\alpha T})}{V_c\alpha(\alpha - \beta)} e^{-\alpha(T+t')} + \frac{k_0(\beta - k_{21})(1 - e^{\beta T})}{V_c\beta(\alpha - \beta)} e^{-\beta(T+t')} \quad \text{(Eq. 6)}$$

Similarly, the drug concentration at time $(T + t')$ after the bolus dose can be expressed as:

$$C_{p(\text{bolus})} = \frac{X_0(\alpha - k_{21})}{V_c(\alpha - \beta)} e^{-\alpha(T+t')} + \frac{X_0(k_{21} - \beta)}{V_c(\alpha - \beta)} e^{-\beta(T+t')} \quad \text{(Eq. 7)}$$

where t' is the elapsed time after termination of the infusion.

Equations 6 and 7 can be combined to obtain plasma drug levels at the end of an infusion, $C_{p(\text{post})}$, when simultaneous intravenous priming and infusion doses are administered. Combining Eqs. 6 and 7 and simplifying yield:

$$C_{p(\text{post})} = C_{p(\text{bolus})} + C_{p(\text{inf})} = \frac{\alpha - k_{21}}{V_c(\alpha - \beta)} \times \left[X_0 - \frac{k_0}{\alpha}(1 - e^{\alpha T})\right] e^{-\alpha(T+t')} + \frac{k_{21} - \beta}{V_c(\alpha - \beta)} \left[X_0 - \frac{k_0}{\beta}(1 - e^{\beta T})\right] e^{-\beta(T+t')} \quad \text{(Eq. 8)}$$

Combining Eqs. 2, 3, and 8 and rearranging yield:

$$C_{p(\text{post})} = \frac{A}{X_0}\left[X_0 - \frac{k_0}{\alpha}(1 - e^{\alpha T})\right] e^{-\alpha T}e^{-\alpha t'} + \frac{B}{X_0}\left[X_0 - \frac{k_0}{\beta}(1 - e^{\beta T})\right] e^{-\beta T}e^{-\beta t'} \quad \text{(Eq. 9)}$$

or:

$$C_{p(\text{post})} = \frac{A}{X_0}\left[X_0e^{-\alpha T} + \frac{k_0}{\alpha}(1 - e^{-\alpha T})\right] e^{-\alpha t'} + \frac{B}{X_0}\left[X_0e^{-\beta T} + \frac{k_0}{\beta}(1 - e^{-\beta T})\right] e^{-\beta t'} \quad \text{(Eq. 10)}$$

If:

$$\frac{A}{X_0}\left[X_0e^{-\alpha T} + \frac{k_0}{\alpha}(1 - e^{-\alpha T})\right] = A_1 \quad \text{(Eq. 11)}$$

and:

$$\frac{B}{X_0}\left[X_0e^{-\beta T} + \frac{k_0}{\beta}(1 - e^{-\beta T})\right] = B_1 \quad \text{(Eq. 12)}$$

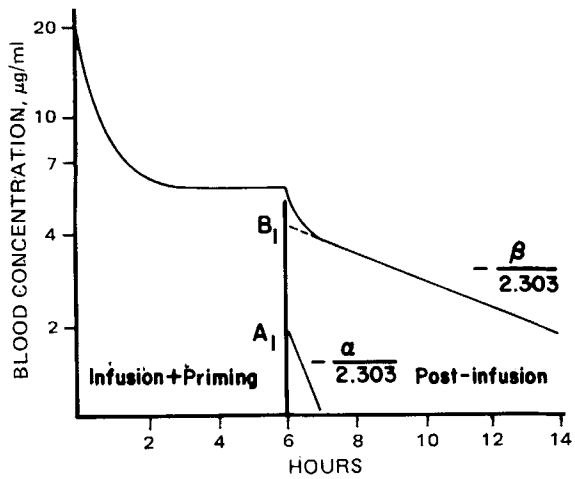


Figure 1—*Simulated blood concentrations after simultaneous administration of intravenous priming and continuous infusion doses of a hypothetical drug.*

then combining Eqs. 10–12 gives:

$$C_{p(\text{post})} = A_1e^{-\alpha t'} + B_1e^{-\beta t'} \quad \text{(Eq. 13)}$$

This equation is equivalent to the biexponential equation defining a rapid intravenous injection blood curve. Thus, when plasma concentrations, $C_{p(\text{post})}$, are plotted semilogarithmically against the postinfusion time, t', a biexponential curve is obtained (Fig. 1).

Parameters A_1, B_1, α, and β can be obtained from these plots, as exemplified in Fig. 1. When these values are known along with X_0, k_0, and T, the intercepts A and B can be computed using Eqs. 11 and 12.

After obtaining A, B, α, and β, various other pharmacokinetic parameters can be calculated by conventional methods (2) as follows:

$$k_{21} = \frac{A\beta + B\alpha}{A + B} \quad \text{(Eq. 14)}$$

$$k_{el} = \frac{\alpha\beta}{k_{21}} \quad \text{(Eq. 15)}$$

$$k_{12} = \alpha + \beta - k_{21} - k_{el} \quad \text{(Eq. 16)}$$

$$AUC = \frac{A}{\alpha} + \frac{B}{\beta} \quad \text{(Eq. 17)}$$

$$V_c = \frac{\text{total dose}}{A + B} \quad \text{(Eq. 18)}$$

$$V_d = \frac{\text{total dose}}{(AUC)\beta} \quad \text{(Eq. 19)}$$

$$Cl_B = V_d\beta \quad \text{(Eq. 20)}$$

where AUC is the area under the plasma level–time curve, V_d is the apparent volume of distribution, Cl_B is the total body clearance, and total dose is the priming plus infusion dose $(X_0 + k_0T)$. All other parameters were defined previously.

Equations 11 and 12 are similar to the corresponding equations (*e.g.*, Eqs. 21 and 22) presented by Loo and Riegelman (1) in their treatment of postinfusion blood level data obtained after an intravenous infusion dose without a simultaneous priming dose:

$$A_1 = \frac{Ak_0(1 - e^{-\alpha T})}{X_0\alpha} \quad \text{(Eq. 21)}$$

and:

$$B_1 = \frac{Bk_0(1 - e^{-\beta T})}{X_0\beta} \quad \text{(Eq. 22)}$$

Three-Compartment Open Model—By using the same treatment for a drug that exhibits the characteristics of a three-compartment open model, the decay of blood levels during the postinfusion period following simultaneous administration of intravenous priming and infusion doses can be expressed as follows:

$$C_{p(\text{post})} = P_1e^{-\pi t'} + A_1e^{-\alpha t'} + B_1e^{-\beta t'} \quad \text{(Eq. 23)}$$

where:

$$P_1 = \frac{P}{X_0}\left[X_0 e^{-\pi T} + \frac{k_0}{\pi}(1 - e^{-\pi T})\right] \quad \text{(Eq. 24)}$$

$$A_1 = \frac{A}{X_0}\left[X_0 e^{-\alpha T} + \frac{k_0}{\alpha}(1 - e^{-\alpha T})\right] \quad \text{(Eq. 25)}$$

$$B_1 = \frac{B}{X_0}\left[X_0 e^{-\beta T} + \frac{k_0}{\beta}(1 - e^{-\beta T})\right] \quad \text{(Eq. 26)}$$

After estimation of P, A, B, π, α, and β, the other pharmacokinetic parameters can be computed using the conventional methods (2) for blood concentration data obtained after a single rapid intravenous injection of the drug.

Occasionally, it is desirable to inject a drug slowly at a constant rate until the desired steady-state blood drug concentration is achieved. However, the time required (about $7 \times t_{1/2\beta}$) to obtain steady-state blood concentrations will be quite long for a drug with a long half-life. It may then be convenient to administer an intravenous priming dose simultaneously with the continuous infusion to obtain steady-state conditions rapidly (3, 4). The relationships derived in this paper are useful for the estimation of pharmacokinetic parameters in these situations.

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Hydrolysis Mechanism of 7-Acetylacroninium Perchlorate, a Novel Prodrug of Acronine

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Abstract □ 7-Acetylacroninium perchlorate was hydrolyzed at 25° by both water enriched with ^{18}O-labeled water and by unenriched water. The acronine obtained was examined by mass spectrometry, which indicated the unusual fact that hydrolysis of this ester proceeded by aryl oxygen cleavage to the extent of about 30% under those mild conditions.

Keyphrases □ 7-Acetylacroninium perchlorate—hydrolysis mechanism □ Acronine prodrug—7-acetylacroninium perchlorate, hydrolysis mechanism □ Prodrugs—7-acetylacroninium perchlorate, hydrolysis mechanism □ Hydrolysis—7-acetylacroninium perchlorate, mechanism determined

The alkaloid acronine[1] (I) has activity against a wide range of tumors (1), but a major problem associated with its administration has been its low water solubility, only about 2–3 mg/liter (2).

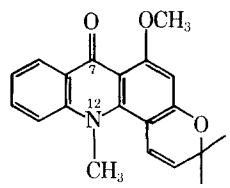
BACKGROUND

Attempts have been made to increase acronine solubility in water by coprecipitating the drug with povidone (3), using a mixture of an organic solvent and water (4), and complexation with various ligands (4). All of these methods failed to increase the water solubility of acronine to a concentration of 30 mg/100 ml, which was the value desired for intravenous administration.

Another approach was based on the fact that, in the presence of acid, protonation of the 7-oxygen of acronine resulted (II) (4). Thus, in preparing an acronine prodrug, acylation of the 7-hydroxy group of an acroninium salt would be expected to produce a 7-acyloxyacroninium salt with increased water solubility compared to acronine and yet be capable of regenerating acronine *in vivo*. 7-Acetylacroninium perchlorate (III) was prepared and is over 100 times more water soluble than acronine; *in vitro*, it is converted quantitatively to acronine. However, the prodrug suffers from the disadvantage of being hydrolyzed too rapidly [$t_{1/2} \sim 20$ min under ambient temperatures (18–25°) in nonirritating, nontoxic, and water-miscible media] to be of clinical use (5).

The rapid solvolysis of III may be due, in part, to aryl oxygen fission, since modification of the alkyl moiety of the ester group of analogs of III reportedly yielded compounds with nearly identical hydrolysis rates (4). In addition, the reaction of III with both aniline and mercaptide ions resulted in the formation of the corresponding 7-anil and 7-thioketones.

The purpose of this work was to determine whether hydrolysis by aryl oxygen fission would occur to an appreciable extent under mild conditions. Such information is of interest from a general standpoint and might also prove useful in the design of related prodrugs with improved stability properties.



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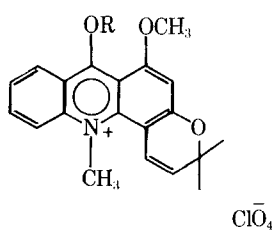

II: R = H
III: R = $COCH_3$

[1] Referred to as acronycine previously.