Assessment of Pharmacokinetic Constants from Postinfusion Blood Curves Obtained after I.V. Infusion

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Abstract □ Pharmacokinetic constants have usually been derived from the parameters of the exponential equation which describe the blood curve after a single bolus i.v. injection. Occasionally, due to potential toxicity, irritation, or limited solubility, it is not possible to inject a drug by a single bolus; it may be feasible to circumvent these difficulties by administering the drug intravenously at a slower rate of infusion. A mathematical equation is presented which enables one to determine the parameters identical to an i.v. bolus injection curve by utilizing the postinfusion blood curve. The equation is applicable to all compartmental models that may be described by linear first-order differential equations with constant coefficients. Experimental data are presented whereby drugs were administered by very rapid and prolonged i.v. infusion with blood sampling at appropriate intervals. The experimentally estimated parameters calculated from the postinfusion blood curves were in agreement with those obtained from the rapid infusion blood curves.

Keyphrases □ Pharmacokinetic constants determination—postinfusion curves □ Kinetic equations—slow i.v. infusion □ Griseofulvin—slow, rapid i.v. infusion □ Sulfisoxazole—slow, rapid i.v. infusion

Pharmacokinetic parameters are usually derived from the exponential equations which describe the blood curve after a single bolus i.v. injection. Occasionally, due to potential toxicity, irritation, or limited solubility, it is not possible to inject a drug by a single bolus. It may be feasible to circumvent these difficulties by administering the drug intravenously at a slower rate of infusion. An equation is derived below which enables one to determine the parameters identical to those obtained from an i.v. bolus injection curve by utilizing the postinfusion blood level *versus* time curve. The equation is applicable to all compartment models describable by linear first-order differential equations with constant coefficients. Experimental data will be presented from studies in which drugs were administered by very rapid and prolonged i.v. infusion into man and rabbit.

THEORETICAL

If drug elimination and distribution processes obey first-order kinetics then the blood curve, after a single bolus i.v. injection, is describable by a summation of exponential terms.

$$(Cp)_{\text{i.v.}} = \sum_{i=1}^{n} A_i e^{-k_i t} \qquad \text{(Eq. 1)}$$

where $(Cp)_{\text{i.v.}}$ represents the plasma concentration[1] at time t, after administration of the i.v. dose, A_i is the intercept at zero time, and k_i is the corresponding first-order rate constant as defined in Eq. 1. The Laplace transform of Eq. 1 is

$$\bar{C}p(s) = \sum_{i=1}^{n} \frac{A_i}{(s + k_i)} = f_1(s) \qquad \text{(Eq. 2)}$$

where $\bar{C}p$ represents the Laplace transform of Cp. If the same dose of the drug is infused continuously at a constant rate (k_0) (see Footnote 2) until time τ, then ceased abruptly, the Laplace transform for this input function is:

$$f_2(s) = \frac{k_0}{s}(1 - e^{-\tau s}) \qquad \text{(Eq. 3)}$$

where $f_2(s)$ is the step function of height k_0 starting at zero-time and stopping at $t = \tau$. The Laplace transform (1) of the postinfusion curve is the product of the input function $f_2(s)$ and the unit impulse function $f_1(s)$.

$$(\bar{C}p)_{\text{post}}(s) = f_1(s) \cdot f_2(s) \qquad \text{(Eq. 4)}$$

$(\bar{C}p)_{\text{post}}$ denotes the Laplace transform of the plasma concentration when $t > \tau$. Substituting Eqs. 2 and 3 for $f_1(s)$ and $f_2(s)$, respectively, one obtains:

$$(\bar{C}p)_{\text{post}}(s) = \frac{k_0}{s}(1 - e^{-\tau s})\left[\sum_{i=1}^{n} \frac{A_i}{s + k_i}\right] \qquad \text{(Eq. 5)}$$

Separating terms we arrive at:

$$(\bar{C}p)_{\text{post}}(s) = \frac{k_0}{s}\left[\sum_{i=1}^{n} \frac{A_i}{s + k_i}\right] - \frac{k_0}{s} e^{-\tau s}\left[\sum_{i=1}^{n} \frac{A_i}{s + k_i}\right] \qquad \text{(Eq. 6)}$$

The antitransform of Eq. 6 at times greater than τ is

$$(Cp)_{\text{post}} = k_0\left[\sum_{i=1}^{n} \frac{A_i}{k_i} - \sum_{i=1}^{n} \frac{A_i}{k_i} e^{-k_i t} - \sum_{i=1}^{n} \frac{A_i}{k_i} + \sum_{i=1}^{n} \frac{A_i}{k_i} e^{-k_i(t-\tau)}\right] \qquad \text{(Eq. 7)}$$

Upon simplification of Eq. 7, we have:

$$(Cp)_{\text{post}} = k_0\left[\sum_{i=1}^{n} \frac{A_i}{k_i} e^{-k_i(t-\tau)} - \sum_{i=1}^{n} \frac{A_i}{k_i} e^{-k_i t}\right] \qquad \text{(Eq. 8)}$$

Substituting τ for k_0 and setting $t' = (t - \tau)$ upon simplifying Eq. 8, one gets[3]

$$(Cp)_{\text{post}} = \sum_{i=1}^{n} \frac{A_i(1 - e^{-k_i\tau})}{k_i\tau} e^{-k_i t'} \qquad \text{(Eq. 9)}$$

When the infusion time is sufficiently short such that $\sum_{i=1}^{n}(1 - e^{-k_i\tau})$ approaches $\sum_{i=1}^{n} k_i\tau$, Eq. 9 reduces to:

$$(Cp)_{\text{post}} = \sum_{i=1}^{n} A_i e^{-k_i t'} \qquad \text{(Eq. 10)}$$

This equation is equivalent to the equation defining an i.v. bolus injection blood curve. However, when the infusion time is sufficiently

[1] The plasma concentration could be expressed as the concentration of the free drug and/or its metabolite.

[2] k_0 is expressed as the fractional infusion rate and is equal to amount infused per unit time/amount of dose administered = (infusion time)$^{-1}$.

[3] This is a general solution for the postinfusion curves pertaining to all multicompartment model systems. However, an equation for the special two-compartment model case has been derived previously by Rescigno and Segre (7).

Table I—The Biexponential Equations[a] Describing the Postinfusion Curves Obtained after Rapid and Prolonged Administration of Sulfisoxazole Intravenously into a Male Rabbit

Infusion Time	A_1'	k_1	A_2'	k_2	Error Mean Square
10 sec.					
Experimental[b] values	57.3 ± 2.6[c]	0.1244 ± 0.0099	42.7 ± 2.5	0.01115 ± 0.00091	1.5485
30 min.					
Experimental values	33.0 ± 2.3	0.1286 ± 0.0171	67.3 ± 2.2	0.00982 ± 0.00047	1.2027
Calculated[d] values	29.3	0.1244 ± 0.0099	70.7	0.01115 ± 0.00091	
60 min.					
Experimental values	22.8 ± 2.6	0.1338 ± 0.0278	77.2 ± 2.5	0.01018 ± 0.00056	1.5563
Calculated values	19.8	0.1244 ± 0.0099	80.2	0.01115 ± 0.00091	

[a] The equation is : $P\% = A_1e^{-k_1t} + A_2e^{-k_2t}$. A_1, A_2, and $P\%$, are expressed in percentage of $(A_1 + A_2)$. k_1, k_2 are expressed in reciprocal minutes. t is the time after infusion in minutes. [b] These values were determined from the experimental data by using an IBM 360/50 digital computer programmed according to a nonlinear regression subroutine of the B.M.D. X85 series. [c] Standard deviation units. [d] These values were generated from Eq. 9 by using the parameters of the postinfusion curves after the fastest infusion experiment.

long such that $\sum_{i=1}^{n} (1 - e^{-k_i\tau'})$ approaches n, Eq. 9 becomes:

$$(Cp)_{post} = \sum_{i=1}^{n} \frac{A_i}{k_i\tau} e^{-k_it'} \qquad \text{(Eq. 11)}$$

It is evident from these considerations that k_i is the same whether it is obtained from a postinfusion curve or a single i.v. bolus curve. However, the intercepts of the exponential terms (*i.e.*, A_i and $A_i[(1 - e^{-k_it})/(k_i\tau)]$) are different and the differences increase as the infusion time lengthens. Since these intercepts are used to calculate kinetic constants intrinsic to multicompartmental models, an appropriate correction must therefore be made. The intercepts can be calculated from the following equation:

$$A_i = \frac{k_i\tau}{1 - e^{-k_i\tau}} A_i' \qquad \text{(Eq. 12)}$$

where A_i' is the intercept, extrapolated to $t' = 0$, obtained from the postinfusion curve. Incorporating Eq. 12 into Eq. 1, we arrive at the following equation:

$$(Cp)_{i.v.} = \sum_{i=1}^{n} \frac{k_i\tau}{1 - e^{-k_i\tau}} A_1' e^{-k_it} \qquad \text{(Eq. 13)}$$

Thus, an equation has been derived which will lead to the same parameters as obtained after a single i.v. bolus injection. If the parameters were obtained from free drug plasma concentration *versus* time curve, then the kinetic and volume constants intrinsic to the compartmental model can be calculated by procedures previously described[4] (2, 3). However if the parameters were de-

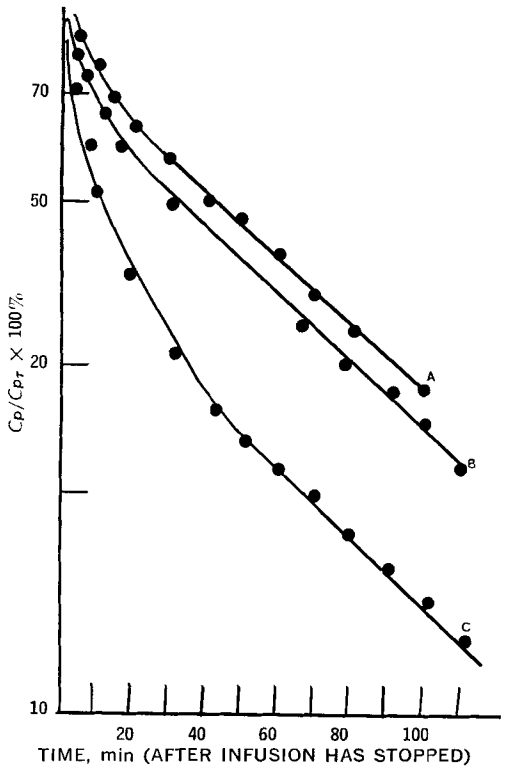

Figure 1—*Sulfisoxazole plasma level after intravenous infusion into rabbit. Key:* A, *after an infusion time period,* τ, *of 60 min.;* B, *after 30-min. infusion;* C, *after 10-sec. infusion;* Cp, *plasma concentration* after *infusion has stopped;* Cp_τ, *plasma concentration at the end of the infusion. The use of* Cp/Cp_τ *normalizes the data allowing more convenient comparison of data among the experiments.*

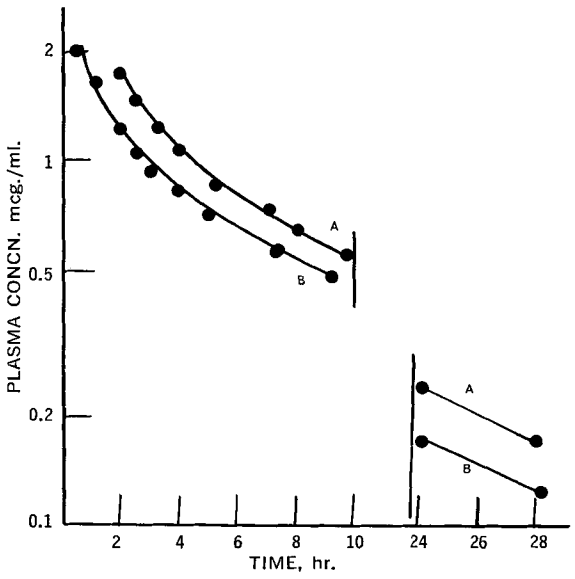

Figure 2—*Griseofulvin plasma level after intravenous infusion into man. Key:* A, *plasma level after 3-min. infusion;* B, *plasma level after 2-hr. infusion.*

[4] In *Reference* 3 the equation for the $Vd°$ is in error. The correct equation should be $Vd° = Vd_{ss} = Vp\ (k_{21} + k_{12}/(k_{21}) = Vd$ infusion. This error has been pointed out to the authors by Gibaldi (4).

Table II—The Biexponential Equations[a] Describing the Postinfusion Curves Obtained after Rapid and Prolonged Intravenous Administration of Griseofulvin into a Male Human Subject

Dose	Infusion Time		A_1'	k_1	A_2'	k_2	Error Mean Square
142 mg.	3 min.	Experimental values	1.492 ± 0.046	0.7032 ± 0.0510	0.9854 ± 0.0486	0.07252 ± 0.00499	0.0039
153.6 mg.	2 hr.	Experimental values	0.7101 ± 0.0877	0.7677 ± 0.1825	1.0631 ± 0.0884	0.06377 ± 0.00761	0.0170
		Calculated values	0.8664	0.7032 ± 0.0510	0.9921	0.07252 ± 0.00499	

[a] All terms and values as denoted in Table I except A_1', A_2', are expressed in micrograms per milliliters. k_1, k_2 are expressed in reciprocal hours.

rived from the metabolite or total drug concentration *versus* time curve then different procedures must be developed to calculate these constants.

EXPERIMENTAL PROCEDURE

Griseofulvin—Griseofulvin was injected into a healthy male adult in a specially prepared solution of griseofulvin dissolved in polyethylene glycol 300. The solution was not injected directly. It was diluted into a rapidly flowing normal saline solution, which was administered by intravenous drip over a 3-min. period. Several weeks later the drug was administered over a 2-hr. interval at a constant rate of infusion into the same test subject. The plasma samples were assayed for the intact drug by a modification of the method of Bedford *et al.* (5).

Sulfisoxazole—The left and right marginal ear veins of a male rabbit (4.5 kg.) were cannulated by small catheters (Bardic Intracath Cat. No. 1619 small catheters 20.32 cm. (8 in.), i.d. 0.015 mm.). Sulfisoxazole injection (Roche) was diluted to an appropriate volume with sterile normal saline solution and then infused into the left vein by means of a constant infusion pump. Blood samples were then withdrawn from the right cannula. The catheters were removed from the ear veins after the experiments. The rabbits were utilized for additional experiments after their ear veins had properly healed. The plasma samples were assayed for sulfonamide (unconjugated at the N_4 position) using the Bratton and Marshall procedure (6).

RESULTS AND DISCUSSION

The rapid infusion or the single bolus i.v. blood curves are describable by the following biexponential equation:

$$Cp_{\text{i.v.}} = A_1e^{-k_1t} + A_2e^{-k_2t} \qquad \text{(Eq. 14)}$$

By applying Eq. 9 to Eq. 14, one gets

$$(Cp)_{\text{post}} = \frac{A_1(1 - e^{-k_1\tau})}{k_1\tau} e^{-k_1t'} + \frac{A_2(1 - e^{-k_2\tau})}{k_2\tau} e^{k_2t'} \qquad \text{(Eq. 15)}$$

or

$$(Cp)_{\text{post}} = A_1'e^{-k_1t'} + A_2'e^{-k_2t'} \qquad \text{(Eq. 16)}$$

where A_1' and A_2' are definable from Eq. 15; Figs. 1 and 2 represent the experimental data obtained on griseofulvin and sulfisoxazole. The experimentally determined A_1', A_2', k_1', k_2', and the corresponding values as calculated from Eq. 9 are summarized in Tables I and II.

The experimental data points were initially fitted to biexponential equations by the use of an E.A.I. T.R. 48 analog computer. The experimental data together with the initial estimated parameters were then refitted or reassessed with an IBM 360/50 computer programmed in accordance with a modified nonlinear least-squares regression subroutine of the B.M.D. X85 series.

The theoretical A_1' and A_2' were calculated using A_1, A_2, k_1, and k_2 values obtained from the single i.v. bolus or rapid infusion curves.

The satisfactory correlation between the experimental values and the calculated values are evident. Most of the experimental values are within one standard deviation of the calculated values. All of the experimental values are within two standard deviations of the calculated values. From Tables I and II it is seen that the ratio A_1'/A_2' decreases as the infusion time increases. This observation is in accordance with Eq. 9. Since $k_1 > k_2$, the value $A_1(1 - e^{-k_1\tau})/(k_1\tau)$ will decrease more rapidly with increasing τ than the value for $A_2(-e^{k_2\tau})/(k_2\tau)$ thus accounting for the above observation.

From Fig. 1 it is seen that the changes in the intercept ratio are also reflected by the decreasing degree of the initial curvature of the blood curve with increasing infusion time. Since this curved region is critical to the definition of the multicompartmental pharmacokinetic parameters, sampling must be sufficiently frequent to characterize adequately this region of the blood curve, especially if the infusion is prolonged. It is, therefore, advisable to minimize the infusion time not only for the convenience of the subject, but also to reduce the necessity for frequent sampling.

In Fig. 2 the data points lie close to the theoretical line as calculated from the single i.v. bolus parameters. The change in the initial curvature is not so apparent visually from the *Cp versus t* curve. However, the computer-analyzed data given in Table II show a drastic change in the intercept A_1 and very little change in the intercept A_2. This is quite in accord with Eq. 15. The graphical representations given in Figs. 1 and 2 are for illustrative purposes only and should not be used for final estimation of the parameters of the equation in lieu of a computer solution.

The findings reported in this study suggest that in multicompartmental pharmacokinetic studies the post infusion curve can be utilized to obtain pharmacokinetic parameters in lieu of the more conventional single i.v. bolus injection. This infusion procedure is especially useful when one encounters potential difficulties, such as solubility and toxicity.

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ACKNOWLEDGMENTS AND ADDRESSES

Received June 4, 1969 from the *Departments of Pharmacy and Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco Medical Center, San Francisco, CA 94122*

Accepted for publication August 26, 1969.

Presented to the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, Montreal meeting, May 1969.

This research was supported in part by a grant-in-aid from the research funds of the Academic Senate, San Francisco Division, University of California.