Kinetics of Pharmacological Effects on Constant-Rate Intravenous Infusion

Keyphrases □ Pharmacokinetics—mathematical method for analysis of pharmacological effects on constant-rate intravenous drug infusion □ Mathematics—method for analysis of pharmacological effects on constant-rate intravenous drug infusion □ Kinetics—mathematical method for analysis of pharmacological effects on constant-rate intravenous drug infusion

To the Editor:

Over the last 10 years, great interest has developed in monitoring drug and metabolite concentrations in biological fluids to aid in optimizing individual patient drug therapy (1–6). Of course, such drug concentrations are only an indirect index of the ideal monitoring parameter, *i.e.*, pharmacological response. The theoretical bases for quantifying pharmacological response for reversible pharmacodynamic processes were examined thoroughly (7–10). These mathematical relationships were used to elucidate the kinetics of the pharmacological effect of tubocurarine (11–14), succinylcholine (15–17), lysergide (18–20), mercaptomerin (21), ethanol (22), warfarin (23, 24), theophylline (25), and cocaine (26). Each of these drugs elicits a pharmacological effect that can be accurately and reproducibly quantified. This report describes a method for elucidating pharmacokinetic properties following constant-rate intravenous infusion of drugs eliciting quantifiable, reversible pharmacological responses that are immediate, not delayed, effects.

The linear portion of the classic log concentration–response relationship can be described by (7):

$$E = m \log C + e \qquad \text{(Eq. 1)}$$

where C is the concentration, E is the response, m is the slope of the linear portion of E *versus* log C, and e is the unit concentration intercept of E *versus* log C. With the assumption of instantaneous drug distribution and first-order drug elimination, plasma drug concentration during constant-rate intravenous infusion can be described by the following function of time:

$$C = \frac{k_0}{Cl}(1 - e^{-Kt}) \qquad \text{(Eq. 2)}$$

where k_0 is the zero-order infusion rate, Cl is the total body clearance, K is the first-order elimination rate constant, and t is time.

Substitution of Eq. 2 into Eq. 1 provides the relationship describing the pharmacological effect as a function of time during ongoing intravenous infusion:

$$E = m \log \frac{k_0}{Cl}(1 - e^{-Kt}) + e \qquad \text{(Eq. 3a)}$$

or:

$$E = m \log k_0 - m \log Cl + m \log (1 - e^{-Kt}) + e \qquad \text{(Eq. 3b)}$$

As infusion continues toward steady state, the term e^{-Kt} approaches zero. Therefore, at steady state, Eq. 3*b* becomes:

$$E_{ss} = m \log k_0 - m \log Cl + e \qquad \text{(Eq. 4a)}$$

where E_{ss} is the pharmacological effect at steady state. This relationship is most useful following conversion to the form:

$$E_{ss} = m \log k_0 - b \qquad \text{(Eq. 4b)}$$

where $b = m \log Cl - e$; b is the y intercept of E_{ss} *versus* log k_0.

For a drug satisfying the prior assumptions, Eq. 4*b* indicates that a plot of the steady-state pharmacological effect *versus* the logarithm of the intravenous zero-order infusion rate is linear with a slope equal to m, the slope of the linear portion of the log concentration–response relationship.

Consider the time course of declining pharmacological effect. Rearrangement of Eq. 1 yields:

$$\log C = \frac{E - e}{m} \qquad \text{(Eq. 5)}$$

Postinfusion, monoexponential decline of the plasma drug concentration from the steady-state concentration (C_{ss}) achieved *via* constant-rate intravenous infusion is described by:

$$\log C = \log C_{ss} - \frac{Kt}{2.303} \qquad \text{(Eq. 6)}$$

Substituting for log C and log C_{ss} in Eq. 6 from Eq. 5 yields:

$$\frac{E - e}{m} = \frac{E_{ss} - e}{m} - \frac{Kt}{2.303} \qquad \text{(Eq. 7a)}$$

or:

$$E = E_{ss} - \frac{mK}{2.303}t \qquad \text{(Eq. 7b)}$$

Equation 7*b* indicates that a plot of postinfusion pharmacological effect *versus* time declines linearly from steady state, with the slope providing an estimate of the product of K and m. Construction of plots of E_{ss} *versus* log k_0 (Eq. 4*b*) and E *versus* time, for effect declining from steady state (Eq. 7*b*), provides estimates of m and mK, respectively, and thereby enables estimation of K. But knowing K, the biological half-life ($t_{1/2}$) is readily calculated from:

$$t_{1/2} = \frac{\ln 2}{K} \qquad \text{(Eq. 8)}$$

In addition to the assumptions stated in the original papers on this type of pharmacological effect model, inference of the pharmacokinetic behavior of a drug based on pharmacological effect data requires that no metabolites have measurable interfering pharmacological activity (27). If the decline of pharmacological effect is rate limited by the drug diffusion rate from the site of action, the reformation rate of an essential enzyme, or homeostatic control mechanisms, the apparent elimination rate constant calculated from the equations discussed in this paper will be representative of the rate-limiting process (11, 28).

This method was applied to data obtained from a previous study (29). In that study, 54 patients in a state of hypertensive emergency received sodium nitroprusside infusions in a dose-titration manner to achieve the desired hypotensive effect. Individual data were presented for four

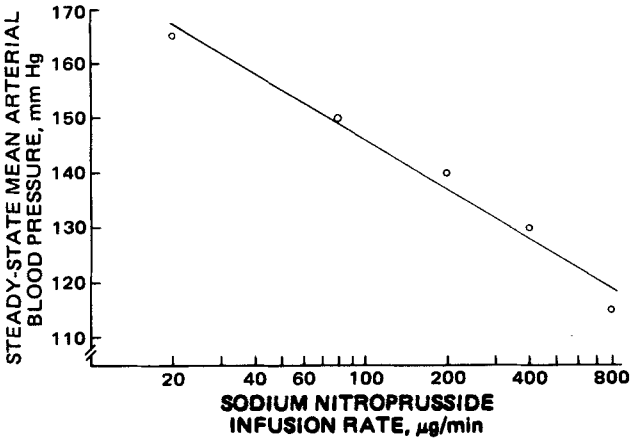

Figure 1—*Relationship between steady-state mean arterial blood pressure and sodium nitroprusside infusion rate in one patient with malignant hypertension. The linear regression line is shown (r = −0.99).*

representative patients. Data on one patient, a 45-year-old male with malignant hypertension, renal failure, and congestive heart failure, were presented in sufficient detail to permit the proposed analysis. In accordance with Eq. 4*b*, a linear relationship was obtained between steady-state mean arterial blood pressure and the logarithm of sodium nitroprusside infusion rate over a 40-fold range of zero-order infusion rates (Fig. 1). As shown in Fig. 2, plotting the time course of the hypotensive effect declining from steady state following discontinuation of sodium nitroprusside infusion illustrates adherence to Eq. 7*b*.

Calculation of the slopes in Figs. 1 and 2 provides direct estimates of m and mK of −30.1 mm Hg and 1.40 mm Hg/min, respectively. Therefore, K can be estimated as 0.0465 min^{-1} with a corresponding biological half-life of 14.9 min. This estimate of biological half-life is consistent with the rapidly achieved steady-state hypotensive response observed clinically. This relatively short half-life supports the prior interpretation of the mean arterial blood pressures in Fig. 1 as being reasonable approximations of steady-state values.

This analysis for sodium nitroprusside is exemplary of the potential utility of studying the pharmacokinetic properties of intravenously administered drugs eliciting a quantifiable response. Constant-rate intravenous infusion of a drug having a relatively short biological half-life will enable rapid achievement of steady state at each of the several infusion rates. Although this technique may not be applicable to all drugs, it may provide a basis for practical, exploratory analysis of pharmacological effect data for drugs such as nitroprusside, diazoxide, nitroglycerin, and trimethaphan.

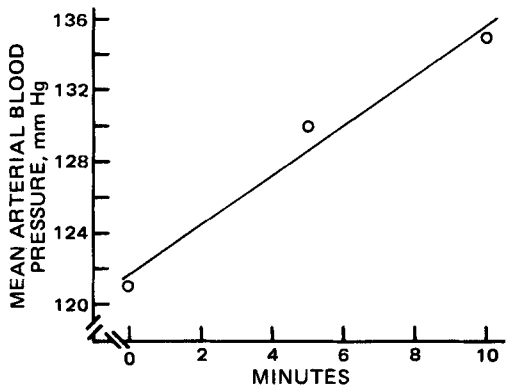

Figure 2—*Time course of increasing mean arterial blood pressure following discontinuation of sodium nitroprusside infusion. The linear regression line is shown (r = 0.99).*

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Plasma Theobromine after Oral Administration of Caffeine to Dogs

Keyphrases □ Theobromine—caffeine metabolite, plasma levels following oral administration of caffeine to dogs □ Caffeine—metabolism in dogs, plasma theobromine levels following oral administration of caffeine to dogs □ Metabolism—of caffeine, plasma levels of metabolite theobromine following oral administration of caffeine to dogs

To the Editor:

Caffeine (1,3,7-trimethylxanthine), a compound in coffee, tea, and many other beverages, has been used successfully for the treatment of apnea in premature infants