Errors Involved in Instantaneous Intravascular Input Assumptions

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Abstract □ A comparative evaluation of a zero-order input and the generally accepted instantaneous intravascular input assumption is made for two- and three-compartment open model systems. Equations are derived and a nomogram is prepared to calculate the magnitude of error involved in instantaneous input assumptions. It is suggested that all intravascular administrations be considered as zero-order inputs.

Keyphrases □ Pharmacokinetic models—errors in instantaneous intravascular input assumptions, two- and three-compartment open models □ Disposition, drug—pharmacokinetic models, errors in instantaneous intravascular input assumptions, two- and three-compartment open models

Pharmacokinetic modeling of drug disposition frequently has been used to characterize dosage regimens, toxicity profiles, and pharmacological responses (1–5). The pharmacokinetic parameters such as various compartment volume terms and the rate constants describing the intercompartmental transfer and elimination from the body often have been appropriately determined by quickly administering an intravascular dose and assuming that all of the drug is present in the central compartment when the kinetic processes of distribution and elimination begin (2).

Although the assumption of instantaneous intravascular administration simplifies the model, a detailed description of the model, including the kinetic processes during the period of administration, would eliminate possible errors due to this assumption. Also, this model can be used in instances where a prolonged administration is necessary to build up analyzable concentrations in the blood. The purposes of this paper are to evaluate comparatively the pharmacokinetic models with zero-order and instantaneous input and to offer a critique on the magnitude of error involved in the instantaneous intravascular input assumption.

THEORY

The disposition kinetics of many drugs can be more appropriately described in terms of multicompartment models than by assuming the body to be a single compartment (4) as depicted in Schemes I and II for the most commonly encountered two- and three-compartment open models. The kinetics of these models were analyzed assuming instantaneous input (6).

The time course of drug disposition following zero-order infusion in a two-compartment open model (Scheme I) was reported (2, 6):

$$\frac{x_1}{k_0} = \frac{(k_{21} - b_1)(1 - e^{-b_1\theta})}{b_1(b_2 - b_1)} e^{-b_1 t'} - \frac{(k_{21} - b_2)(1 - e^{-b_2\theta})}{b_2(b_2 - b_1)} e^{-b_2 t'} \quad \text{(Eq. 1)}$$

$$\frac{x_2}{k_0} = \frac{k_{12}(1 - e^{-b_1\theta})}{b_1(b_2 - b_1)} e^{-b_1 t'} - \frac{k_{12}(1 - e^{-b_2\theta})}{b_2(b_2 - b_1)} e^{-b_2 t'} \quad \text{(Eq. 2)}$$

where:

x_1, x_2 = amounts in the central and tissue compartments, respectively
b_1, b_2 = hybrid rate constants
k_0 = zero-order infusion rate
θ = duration of infusion
$t' = (t - \theta)$, time following infusion

A three-compartment open model with zero-order input is shown in Scheme II. A kinetic description of this model is:

$$\frac{dx_1}{dt} = k_0 + k_{21}x_2 + k_{31}x_3 - k_{12}x_1 - k_{13}x_1 - k_{el}e_1 \quad \text{(Eq. 3)}$$

$$\frac{dx_1}{dt} = k_0 + k_{21}x_2 + k_{31}x_3 - k_1x_1 \quad \text{(Eq. 4)}$$

$$\frac{dx_2}{dt} = k_{12}x_1 - k_{21}x_2 \quad \text{(Eq. 5)}$$

$$\frac{dx_3}{dt} = k_{13}x_1 - k_{31}x_3 \quad \text{(Eq. 6)}$$

with the conditions $x_1 = x_2 = x_3 = 0$ at $t = 0$. By using Laplace transforms, one can write:

$$(S + k_1)X_1 - k_{21}X_2 - k_{31}X_3 = k_0/S \quad \text{(Eq. 7)}$$

$$-k_{12}X_1 + (S + k_{21})X_2 = 0 \quad \text{(Eq. 8)}$$

$$-k_{13}X_1 + (S + k_{31})X_3 = 0 \quad \text{(Eq. 9)}$$

where X_1, X_2, and X_3 are Laplace transforms of x_1, x_2, and x_3, respectively.

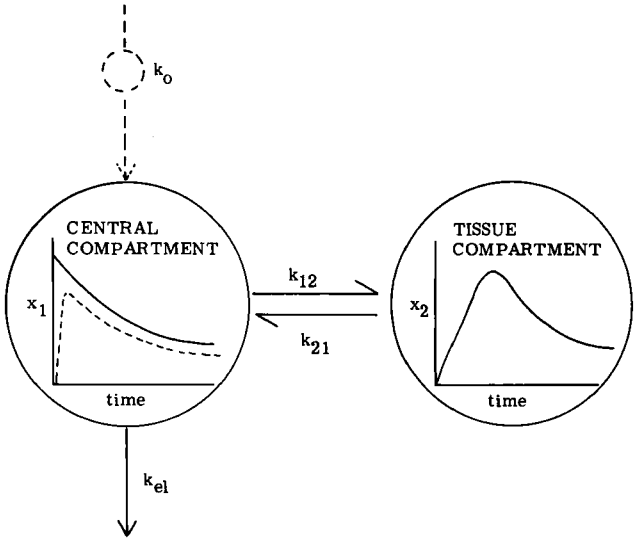
When no complex roots are assumed:

$$\Delta = S(S + b_1)(S + b_2)(S + b_3) \quad \text{(Eq. 10)}$$

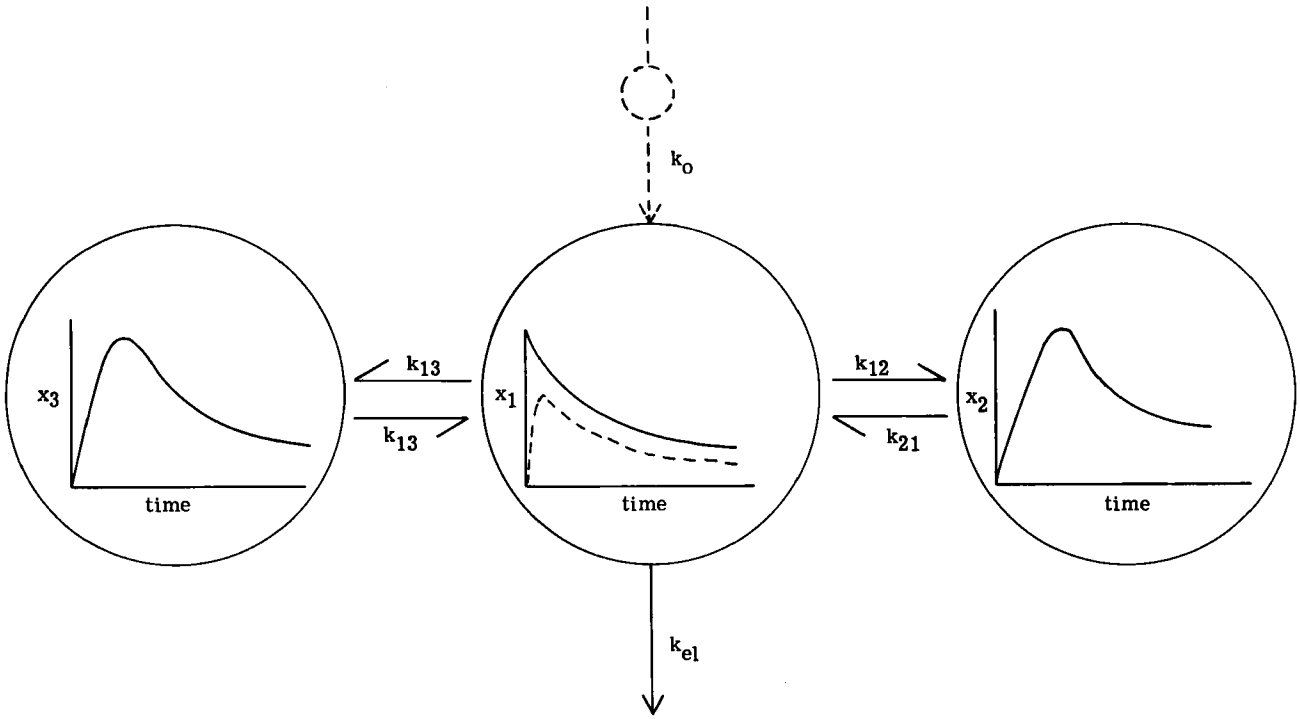
$$\Delta_{1,1} = k_0(S + k_{21})(S + k_{31}) \quad \text{(Eq. 11)}$$

$$\Delta_{1,2} = -k_0k_{12}(S + k_{31}) \quad \text{(Eq. 12)}$$

$$\Delta_{1,3} = k_0k_{13}(S + k_{21}) \quad \text{(Eq. 13)}$$



Scheme I—Two-compartment open model with instantaneous or zero-order input



Scheme II—Three-compartment open model with instantaneous or zero-order input

and by Cramer's rule:

$$\frac{X_1}{k_0} = \frac{\Delta_{1,1}}{\Delta} = \frac{(-1)^2(S + k_{21})(S + k_{31})}{S(S + b_1)(S + b_2)(S + b_3)} \quad \text{(Eq. 14)}$$

$$\frac{X_2}{k_0} = \frac{\Delta_{1,2}}{\Delta} = -\frac{(-1)^3 k_{12}(S + k_{31})}{S(S + b_1)(S + b_2)(S + b_3)} \quad \text{(Eq. 15)}$$

$$\frac{X_3}{k_0} = \frac{\Delta_{1,3}}{\Delta} = \frac{(-1)^4 k_{13}(S + k_{21})}{S(S + b_1)(S + b_2)(S + b_3)} \quad \text{(Eq. 16)}$$

with the following solutions:

$$\frac{x_1}{k_0} = \frac{k_{21}k_{31}}{b_1b_2b_3} - \frac{(k_{21} - b_1)(k_{31} - b_1)}{b_1(b_2 - b_1)(b_3 - b_1)}e^{-b_1t} - \frac{(k_{21} - b_2)(k_{31} - b_2)}{b_2(b_1 - b_2)(b_3 - b_2)}e^{-b_2t} - \frac{(k_{21} - b_3)(k_{31} - b_3)}{b_3(b_1 - b_3)(b_2 - b_3)}e^{-b_3t} \quad \text{(Eq. 17)}$$

$$\frac{x_2}{k_0} = \frac{k_{31}k_{12}}{b_1b_2b_3} - \frac{k_{12}(k_{31} - b_1)}{b_1(b_2 - b_1)(b_3 - b_1)}e^{-b_1t} - \frac{k_{12}(k_{31} - b_2)}{b_2(b_1 - b_2)(b_3 - b_2)}e^{-b_2t} - \frac{k_{12}(k_{31} - b_3)}{b_3(b_1 - b_3)(b_2 - b_3)}e^{-b_3t} \quad \text{(Eq. 18)}$$

$$\frac{x_3}{k_0} = \frac{k_{21}k_{13}}{b_1b_2b_3} - \frac{k_{13}(k_{21} - b_1)}{b_1(b_2 - b_1)(b_3 - b_1)}e^{-b_1t} - \frac{k_{13}(k_{21} - b_2)}{b_2(b_1 - b_2)(b_3 - b_2)}e^{-b_2t} - \frac{k_{13}(k_{21} - b_3)}{b_3(b_1 - b_3)(b_2 - b_3)}e^{-b_3t} \quad \text{(Eq. 19)}$$

These equations describe the time course of drug disposition during the infusion period. If the infusion is abruptly ceased following time $t = \theta$, the input function corresponds to a rectangular pulse of length equal to θ. The Laplace transform for such an input is (7):

$$f(S) = \frac{k_0}{S}(1 - e^{-\theta S}) \quad \text{(Eq. 20)}$$

and since:

$$f(S)e^{-\theta S} = f(t - \theta) \quad \text{(Eq. 21)}$$

the functions described in Eqs. 17–19, minus their displaced counterparts by $t' = t - \theta$, describe the time course of drug disposition following the zero-order infusion period:

$$\frac{x_1}{k_0} = \frac{(k_{21} - b_1)(k_{31} - b_1)(1 - e^{-b_1\theta})}{b_1(b_2 - b_1)(b_3 - b_1)}e^{-b_1t'} + \frac{(k_{21} - b_2)(k_{31} - b_2)(1 - e^{-b_2\theta})}{b_2(b_1 - b_2)(b_3 - b_2)}e^{-b_2t'} + \frac{(k_{21} - b_3)(k_{31} - b_3)(1 - e^{-b_3\theta})}{b_3(b_2 - b_3)(b_1 - b_3)}e^{-b_3t'} \quad \text{(Eq. 22)}$$

$$\frac{x_2}{k_0} = \frac{k_{12}(k_{31} - b_1)(1 - e^{-b_1\theta})}{b_1(b_2 - b_1)(b_3 - b_1)}e^{-b_1t'} + \frac{k_{13}(k_{31} - b_2)(1 - e^{-b_2\theta})}{b_2(b_1 - b_2)(b_3 - b_2)}e^{-b_2t'} + \frac{k_{12}(k_{31} - b_3)(1 - e^{-b_3\theta})}{b_3(b_1 - b_3)(b_2 - b_3)}e^{-b_3t'} \quad \text{(Eq. 23)}$$

$$\frac{x_3}{k_0} = \frac{k_{13}(k_{21} - b_1)(1 - e^{-b_1\theta})}{b_1(b_2 - b_1)(b_3 - b_1)}e^{-b_1t'} + \frac{k_{13}(k_{21} - b_2)(1 - e^{-b_2\theta})}{b_2(b_1 - b_2)(b_3 - b_2)}e^{-b_2t'} + \frac{k_{13}(k_{21} - b_3)(1 - e^{-b_3\theta})}{b_3(b_1 - b_3)(b_2 - b_3)}e^{-b_3t'} \quad \text{(Eq. 24)}$$

DISCUSSION

The two-compartment open model was analyzed previously (8–10) incorporating zero-order input. In this paper, the main concerns are the error involved in instantaneous input assumptions in both two-and three-compartment open models and how these errors can be corrected following intravascular drug administration.

The equations presented describing the time course of drug disposition following the administration period can be modified to express the fraction of the administered dose remaining in the central compartment.

For the two-compartment model:

$$\frac{x_1}{k_0\theta} = \frac{(k_{21} - b_1)(1 - e^{-b_1\theta})}{b_1(b_2 - b_1)\theta}e^{-b_1t'} + \frac{(b_2 - k_{21})(1 - e^{-b_2\theta})}{b_2(b_2 - b_1)\theta}e^{-b_2t'} \quad \text{(Eq. 25)}$$

For the three-compartment model:

$$\frac{x_1}{k_0\theta} = \frac{(k_{21} - b_1)(k_{31} - b_1)(1 - e^{-b_1\theta})}{b_1(b_2 - b_1)(b_3 - b_1)\theta}e^{-b_1t'} + \frac{(k_{21} - b_2)(k_{31} - b_2)(1 - e^{-b_2\theta})}{b_2(b_1 - b_2)(b_3 - b_2)\theta}e^{-b_2t'} + \frac{(k_{21} - b_3)(k_{31} - b_3)(1 - e^{-b_3\theta})}{b_3(b_2 - b_3)(b_1 - b_3)\theta}e^{-b_3t'} \quad \text{(Eq. 26)}$$

since:

$$k_0\theta = \text{dose administered} \quad \text{(Eq. 27)}$$

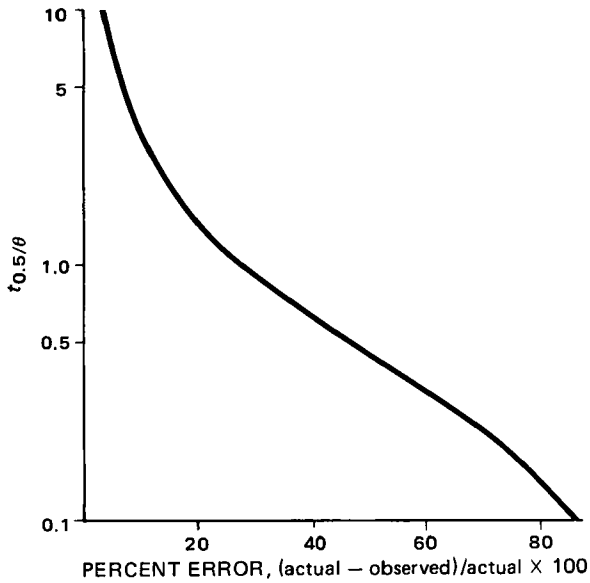


Figure 1—*Percent error involved in the intercept value, assuming instantaneous input at various* $t_{0.5/\theta}$ *ratios.*

A similar treatment of Eqs. 2, 18, and 19 gives the fraction of the administered dose remaining in the tissue compartments. Equations 25 and 26 also represent the ratio of concentration in the central compartment and the concentration at zero time if the total dose is instantaneously administered:

$$\frac{x_1}{k_0\theta} = \frac{c_1 v_1}{c_0 v_1} \qquad \text{(Eq. 28)}$$

where c_1 and c_0 are concentrations in the central compartment, and v_1 is its volume. These equations can be further simplified:

$$\frac{c_1}{c_0} = A_{21}\frac{(1-e^{-b_1\theta})}{b_1\theta}e^{-b_1t'} + A_{22}\frac{(1-e^{-b_2\theta})}{b_2\theta}e^{-b_2t'} \qquad \text{(Eq. 29)}$$

$$\frac{c_1}{c_0} = A_{31}\frac{(1-e^{-b_1\theta})}{b_1\theta}e^{-b_1t'} + A_{32}\frac{(1-e^{-b_2\theta})}{b_2\theta}e^{-b_2t'} + \frac{A_{33}(1-e^{-b_3\theta})}{b_3\theta}e^{-b_3t'} \qquad \text{(Eq. 30)}$$

such that (6) for the two-compartment model:

$$A_{21} + A_{22} = 1 \qquad \text{(Eq. 31)}$$

and for the three-compartment model:

$$A_{31} + A_{32} + A_{33} = 1 \qquad \text{(Eq. 32)}$$

In a model where an instantaneous input assumption is made, it is assumed that:

$$\frac{1 - e^{-b_i\theta}}{b_i\theta} = 1 \qquad \text{(Eq. 33)}$$

where i refers to the disposition phase. This factor is in each term of Eqs. 29 and 30. However, since this fraction (Eq. 33) is always less than 1, c_0 would invariably be underestimated if an instantaneous input is assumed without correcting the intercepts on the concentration–time plot. A reciprocal of Eq. 33 multiplied to the experimental intercept would correct this error. Figure 1 shows the percent error involved as a function of the disposition phase half-life and administration period ratio. A total error can be calculated easily by adding the errors involved in each disposition phase:

$$\text{total error, \%} = 100\sum_{i=1}^{n}\frac{\theta b_i - 1 + e^{-b_i\theta}}{\theta b_i} \qquad \text{(Eq. 34)}$$

For example, a detailed pharmacokinetic analysis of fluorocarbon aerosol propellants (11) showed that the blood concentration profile of dichlorodifluoromethane can be given by:

$$c_1 = 2379.6e^{-0.49499t} + 362.9e^{-0.08941t} + 18.2e^{-0.01026t} \qquad \text{(Eq. 35)}$$

following the administration of the fluorocarbon over 3 min. The cumulated error involved, from Fig. 1, is 62% if proper corrections are not made in the calculations. Therefore, the corrected equation should read:

$$c_1 = 4568.4e^{-0.49499t} + 413.7e^{-0.08941t} + 18.5e^{-0.01026t} \qquad \text{(Eq. 36)}$$

It is obvious that an instantaneous input assumption will always result in an error which can be easily corrected if the data are treated considering the intravascular administration as a zero-order input (Schemes I and II). Such modification is necessary to make the pharmacokinetic model more realistic, since there is no provision of a lag time in a continuous kinetic model.

These models also can be used for drugs that are too poorly soluble or too irritating to be administered by rapid intravenous injection and should be administered slowly over a long period. It is not necessary to achieve an equilibrium for the analysis of pharmacokinetic parameters as was suggested previously (8).

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