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Some methods for estimating absorption rate constant of linear one-compartment open models

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In previous reports methods of estimating absorption rate constant of linear one-compartment open models from peak blood level or peak urinary excretion rate and post-absorptive data have been given (Pidgeon and Pitlick, 1977, 1980; Barzegar-Jalali, 1982a). However, since it is unlikely that the peak values can be observed exactly experimentally, the absorption rate constant obtained from these methods might therefore not be accurate.

In this communication, the parallel line method (Barzegar-Jalali, 1982b) will be applied to the linear one-compartment open models (without or with lag time in absorption) to derive equations from which the absorption rate constant can be estimated from a single data point (for the model without lag time) or two data points (for the model with lag time) at the absorptive phase and postabsorptive data using blood or urine data. Some of the equations can also be employed for graphical determination of the rate constant. Details of the derivation of the equations are as follows.

(1) *The model without lag time in absorption.* The blood level curve for the model is described by Eqn. 1 (Gibaldi and Perrier, 1975)

$$C = \frac{k_a FD}{V(k_a - K)} e^{-Kt} - \frac{k_a FD}{V(k_a - K)} e^{-k_a t} \quad (1)$$

where C is drug concentration in blood at time t, k_a and K are first-order drug absorption and elimination rate constants, respectively, F is fraction of dose D absorbed, and V is the apparent volume of distribution of the drug. A plot of ln C vs t, according to Eqn. 1, will give a bi-exponential curve which will consist of absorptive and elimination phases. The value of k_a is usually greater than the value of K, and therefore, at some time the term $[k_a FD/(k_a - K)V]\, e^{-k_a t}$ will approach zero while the term $[k_a FD/(k_a - K)V]\, e^{-Kt}$ will still have a finite value. Eqn. 1 will

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then reduce to Eqn. 2

$$C = \frac{k_a FD}{V(k_a - K)} e^{-Kt} \tag{2}$$

which in logarithms is

$$\ln C = \ln[k_a FD/V(k_a - K)] - Kt \tag{3}$$

Hence, the value of K can be estimated from the slope of the terminal linear phase (the elimination phase) of the plot and the value of the term $[k_a FD/V(k_a - K)]$ can be estimated from the zero time intercept of the linear phase. In the semilogarithmic bi-exponential blood level plot, the equation of a line drawn from a point at the absorptive phase parallel to the terminal linear phase of the plot (Fig. 1) is

$$\ln C'_t - \ln C_T = -K(t - T) \tag{4}$$

where C'_t is a concentration on the parallel line at time t, C_T is an experimentally determined drug concentration on the absorptive phase of the blood level curve at time T, and K is obtained from Eqn. 3. The value of C'_t can therefore be calculated from Eqn. 5

$$C'_t = C_T e^{-K(t-T)} \tag{5}$$

According to Eqn. 1 the value of C_T is given by

$$C_T = \frac{k_a FD}{V(k_a - K)} e^{-KT} - \frac{k_a FD}{V(k_a - K)} e^{-k_a T} \tag{6}$$

Substituting for C_T from Eqn. 6 into Eqn. 5 and simplification of the resulting equation will yield Eqn. 7

$$C'_t = \frac{k_a FD}{V(k_a - K)} e^{-Kt}[1 - e^{-(k_a - K)T}] \tag{7}$$

But, according to Eqn. 2 the term outside the bracket is equal to C_t (a concentration on the terminal linear phase and/or the extrapolated terminal linear phase at time t). Therefore, Eqn. 7 can be written as Eqn. 8

$$C'_t = C_t[1 - e^{-(k_a - K)T}] \tag{8}$$

Solving Eqn. 8 for k_a will result in Eqn. 9 which can be used for the calculation of k_a value

$$k_a = K - \frac{1}{T} \ln\left(1 - \frac{C'_t}{C_t}\right) \tag{9}$$

where C_t, K, and C'_t are calculated from Eqns. 2, 3 and 5, respectively. It can be shown from Eqns. 2 and 5 that the ratio C'_t/C_t for a given value of T is a constant and is independent of the value of t chosen, provided t corresponds to a concentration at the linear and/or extrapolated linear elimination phase.

Eqn. 9 can also be re-arranged to the following equation for graphical estimation of the k_a value

$$\ln\left(\frac{C_t}{C_t - C'_t}\right) = (k_a - K)T \tag{10}$$

In the values of the left-hand side of Eqn. 10 were determined for different values of T, then a line could be plotted whose slope would be equal to $(k_a - K)$. Since the value of K can be obtained by means of Eqn. 3, the value of k_a is therefore readily calculated from the value of the mentioned slope.

If the special case where the parallel line passes through the peak of the blood level curve its equation will be as follows

$$\ln C'_t - \ln C_{max} = -K(t - t_{max}) \tag{11}$$

or

$$C'_t = C_{max} \cdot e^{-K(t - t_{max})} \tag{12}$$

where C_{max} and t_{max} are the peak blood level and the peak time, respectively. Substituting for C_{max} from the equation $C_{max} = (FD/V)\ e^{-Kt_{max}}$ (Gibaldi and Perrier, 1975) into Eqn. 12 will give:

$$C'_t = \frac{FD}{V}\ e^{-Kt} \tag{13}$$

The concentration, C_t, on the linear phase and/or on the extrapolated linear phase corresponding to t is given by Eqn. 2. Thus, dividing both sides of Eqn. 13 by Eqn. 2 and solving the resulting equation for k_a will result in Eqn. 14

$$k_a = \frac{KC_t}{C_t - C'_t} \tag{14}$$

where C_t, K and C'_t are given by Eqns. 2, 3 and 12, respectively.

It is obvious that, when the parallel line passes through the peak of the blood level curve (i.e. $T = t_{max}$) the right-hand sides of Eqns. 9 and 14 will be equal:

$$K - \frac{1}{t}\ln\left(1 - \frac{C'_t}{C_t}\right) = \frac{KC_t}{C_t - C'_t} \tag{15}$$

or

$$\ln\left(\frac{C_t}{C_t - C_t'}\right) = KT\frac{C_t'}{C_t - C_t'} \tag{16}$$

Eqn. 16 may be of use in determining whether the experimentally observed C_{max} is the actual C_{max} value and therefore for deciding which equation [Eqn. 9 or Eqn. 14 in this report and the equations presented in previous reports (Pidgeon and Pitlick, 1977; 1980; Barzegar-Jalali, 1981a)] must be employed for the calculation of k_a value.

(2) *The model with lag time in absorption.* The blood level for the model is given by Eqn. 17 (Gibaldi and Perrier, 1975)

$$C = \frac{k_a FD}{V(k_a - K)}[e^{-K(t-t_0)} - e^{-k_a(t-t_0)}] \tag{17}$$

where t_0 is a lag time in absorption.

Applying the parallel line method to the model in a similar way discussed above will result in Eqn. 18

$$k_a = K - \frac{1}{T - t_0}\ln\left(1 - \frac{C_t'}{C_t}\right) \tag{18}$$

Re-arrangement of Eqn. 18 gives

$$\ln\left(\frac{C_t}{C_t - C_t'}\right) = (k_a - K)T - t_0(k_a - K) \tag{19}$$

The value of K is calculated from slope of a best-fit line describing the terminal linear phase of the model. C_t is estimated from

$$C_t = \left[\frac{k_a FD\, e^{Kt_0}}{V(k_a - K)}\right] e^{-Kt} \tag{20}$$

where the term $[k_a FD\, e^{Kt_0}/V(k_a - K)]$ is obtained from the zero time intercept of the best-fit line. And C_t' is given by

$$C_t' = C_T\, e^{-K[(t-t_0)-(T-t_0)]} = C_T\, e^{-K(t-T)} \tag{21}$$

in which C_T is an experimentally determined concentration at the absorptive phase at time T.

The slope and intercept of a line resulted from plotting the left-hand side of Eqn. 19 vs T will be equal to $(k_a - K)$ and $-t_0(k_a - K)$, respectively. Since the value of K can be obtained from the slope of the terminal elimination phase, therefore the values of k_a and t_0 can be calculated from the mentioned slope and intercept.

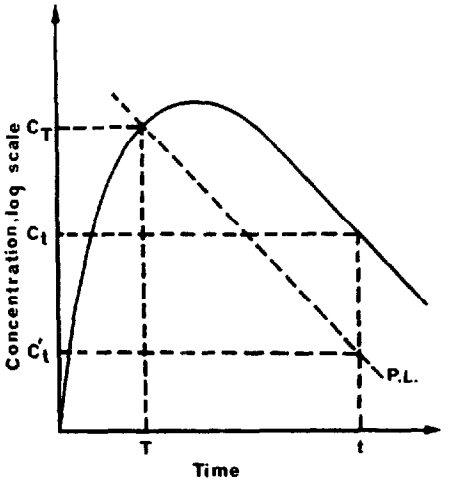

Fig. 1. Semilogarithmic blood level plot of a hypothetical linear one-compartment open model with first-order absorption and the parallel line (P.L.) for presentation of the variables involved in Eqn. 9. See text for the meanings of the symbols.

In the cases where only two data points are available at the absorptive phase, the values of k_a and t_0 are still calculable from two simultaneous equations using Eqn. 18.

The equations obtained from applying the parallel line method to urinary excretion rate equations will be similar to Eqns. 9, 14 and 18 in which $\dot{U}_t$ and $\dot{U}'_t$ (the corresponding excretion rate values) will replace C_t and C'_t.

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