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Short communications

Estimation of parameters of one-compartment open model with constant intravenous infusion using early blood level data

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The available graphical methods for estimating the parameters of the one-compartment open model with a constant intravenous infusion require the blood level data obtained both during and after stopping the infusion. These methods have been discussed by Gibaldi and Perrier (1975) and Wagner (1975). However, in a long-term intravenous infusion of a drug with a low therapeutic index the early estimation of the kinetic parameters of the drug during the infusion might be needed in order to prevent the toxicity.

In this report equations are presented with which it is possible to estimate graphically the elimination rate constant and the steady-state concentration of the drug during the infusion, using early blood level data. Details of the derivation of the equations are as follows.

(a) The plasma concentration, C, of a drug with one-compartment open model during a constant rate infusion is given by Eqn. 1 (Gibaldi and Perrier, 1975):

$$C = \frac{k_0}{KV}(1 - e^{-Kt}) \tag{1}$$

where k_0 is the rate of drug infusion, expressed as amount per unit time, V is the apparent volume of distribution of the drug, K is a first-order elimination rate constant of the drug, and t is time.

The steady-state or plateau concentration, C_{ss}, is given by Eqn. 2 (Gibaldi and Perrier, 1975):

$$C_{ss} = \frac{k_0}{KV} \tag{2}$$

Therefore, Eqn. 1 may be written as:

$$C = C_{ss}(1 - e^{-Kt}) \tag{3}$$

Eqn. 3 is similar to Eqn. 1 given in a previous report (Barzegar-Jalali, 1981) and application of the method of t, 2t, and the method of equal time intervals to Eqn. 3 in a similar way discussed in that report would result in the following graphical equations for estimating K and C_{ss}:

$$\ln\left(\frac{C_t}{C_{2t} - C_t}\right) = Kt \tag{4}$$

$$C_t = C_{ss}\left(2 - \frac{C_{2t}}{C_t}\right) \tag{5}$$

$$\ln(C_{i+1} - C_i) = \ln\left[C_{ss}(1 - e^{-K\Delta t})\right] - Kt_i \tag{6}$$

$$C_i = C_{ss} - \frac{1}{1 - e^{-K\Delta t}}(C_{i+1} - C_i) \tag{7}$$

where C_t, C_{2t}, C_{i+1}, and C_i are the blood levels during the infusion at times t, 2t, $t_i + \Delta t$, and t_i, respectively. The slopes of the plots of the left-hand sides of Eqns. 4 and 5 vs t and $(2 - C_{2t}/C_t)$ would be equal to K and C_{ss}, respectively. Also, the slope of the line resulting from the plot of $\ln(C_{i+1} - C_i)$ vs t_i equals $-K$ (Eqn. 6), and the intercept of the plot of C_i vs $[C_{i+1} - C_i]$ equals C_{ss} (Eqn. 7).

(b) The derivative of Eqn. 3 with respect to time is:

$$\frac{dC}{dt} = KC_{ss} \cdot e^{-Kt} \tag{8}$$

Eqn. 8 in the logarithmic form, i.e.

$$\ln(dC/dt) = \ln(KC_{ss}) - Kt \tag{9}$$

can be used for the graphical estimation of K from the early blood level data. In Eqn. 8 the term dC/dt is the instantaneous rate of change of C with respect to time, but practically one can only determine the average rate, i.e. $\Delta C/\Delta t$. However, application of the method of Martin (1967) to Eqns. 3 and 8 shows that the ratio of the average rate to the instantaneous rate is a constant provided that the blood levels are determined at equal time intervals, Δt, i.e.

$$\lambda = \frac{\Delta C/\Delta t}{dC/dt} \tag{10}$$

and the value of the constant, λ, is given by

$$\lambda = \frac{e^{K\Delta t/2} - e^{-K\Delta t/2}}{K \cdot \Delta t} \tag{11}$$

Therefore, substitution of $(\Delta C/\Delta t)/\lambda$ for (dC/dt) into Eqn. 8 and taking the logarithm of the resulting equation would yield:

$$\ln(\Delta C/\Delta t) = \ln(\lambda K C_{ss}) - Kt \tag{12}$$

Comparison of Eqn. 12 with Eqn. 9 shows that a plot of $\ln(\Delta C/\Delta t)$ vs t (the times at midpoints of the $(\Delta C/\Delta t)$ intervals) would be linear and parallel to a plot of $\ln(dC/dt)$ vs t provided Δt is constant for each point plotted. Consequently, no error will arise in the graphical estimation of K from Eqn. 12 if Δt is constant.

The application of methods of derivations given in a previous report (Barzegar-Jalali, 1981) to Eqn. 3 and its derivatives would result in the following graphical equations for estimating C_{ss}:

$$C_t = C_{ss}\left(1 - \frac{(\Delta C/\Delta t)_{2t}}{(\Delta C/\Delta t)_t}\right) \tag{13}$$

$$C_t = C_{ss} - \frac{1}{\lambda K} \cdot \left(\frac{\Delta C}{\Delta t}\right)_t \tag{14}$$

(c) The equations derived below do not require particular time schemes.

Integration of Eqn. 3 between $t = t'$ and $t = t$ would give Eqn. 15

$$\int_{t'}^{t} C \cdot dt = C_{ss}t + \frac{C_{ss}}{K} \cdot e^{-Kt} - C_{ss}t' - \frac{C_{ss}}{K} e^{-Kt'} \tag{15}$$

According to Eqn. 3 the terms $C_{ss}e^{-Kt}$ and $C_{ss}e^{-Kt'}$ are given by

$$C_{ss}e^{-Kt} = C_{ss} - C_t \tag{16}$$

$$C_{ss}e^{-Kt'} = C_{ss} - C_{t'} \tag{17}$$

Substitution of $C_{ss} \cdot e^{-Kt}$ and $C_{ss} \cdot e^{-Kt'}$ from Eqns. 16 and 17 into Eqn. 15 and simplification and re-arrangement of the resulting equation would give:

$$\frac{\int_{t'}^{t} C \cdot dt}{t - t'} = C_{ss} - \frac{1}{K}\left(\frac{C_t - C_{t'}}{t - t'}\right) \tag{18}$$

where C_t and $C_{t'}$ are blood levels at times t and t′ during the infusion and the integral represents the area under blood level curve between times t′ and t. A plot of the left-hand side of Eqn. 18 vs $(C_t - C_{t'})/(t - t')$ will result in a line whose intercept and slope will equal C_{ss} and $-1/K$, respectively.

Using a similar method of derivation, the following equation can also be obtained from Eqn. 3:

$$\frac{\int_{0}^{t} C \cdot dt}{t} = C_{ss} - \frac{1}{K}\left(\frac{C_t}{t}\right) \tag{19}$$

in which the integral represents the area under blood level curve between times 0 and t.

Once K and C_{ss} are known, the apparent volume of distribution of drug is calculated from Eqn. 20

$$V = \frac{k_0}{KC_{ss}} \tag{20}$$

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