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Short Communications

Some methods for estimating parameters of linear one-compartment open models with bolus intravenous injection and constant rate intravenous infusion using urinary excretion data

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The graphical methods of the determination of parameters of linear one-compartment models with bolus intravenous injection and constant rate intravenous infusion from blood level and urinary excretion data have been discussed by Gibaldi and Perrier (1975) and Wagner (1975). However, the graphical estimation of some of these parameters (e.g. urinary excretion rate constant) following bolus intravenous injection have not been given.

In this communication, methods for estimating the parameters including the urinary excretion rate constant and the infinity value of the cumulative drug amount excreted via urine following bolus intravenous injection into a linear one-compartment open model are presented. Also, a simultaneous method of obtaining the urinary excretion rate constant and the overall elimination rate constant following constant rate intravenous infusion from early urinary excretion data is given. Details of the methods are as follows.

(1) The bolus intravenous injection

(a) The cumulative amount of unchanged drug, U, excreted via urine up to time, t, for the model is given by Eqn. 1 (Gibaldi and Perrier, 1975)

$$U = \frac{k_e D}{K} \cdot (1 - e^{-Kt}) \tag{1}$$

where k_e and K are first-order urinary excretion and elimination rate constants, respectively, and D is the intravenous dose of the drug. The cumulative amount of unchanged drug excreted via urine from times 0 to ∞ (infinity), i.e. U_∞ is given by Eqn. 2 (Gibaldi and Perrier, 1975)

$$U_\infty = \frac{k_e D}{K} \tag{2}$$

Therefore, Eqn. 1 may be written as:

$$U = U_\infty(1 - e^{-Kt}) \tag{3}$$

Eqn. 3 is similar to Eqn. 1 given in a previous report (Barzegar-Jalali, 1981a) 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 will result in the following graphical equations for estimating K and U_∞:

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

$$U_t = U_\infty\left(2 - \frac{U_{2t}}{U_t}\right) \tag{5}$$

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

$$U_i = U_\infty - \frac{1}{1 - e^{-K\Delta t}}(U_{i+1} - U_i) \tag{7}$$

where U_t, U_{2t}, U_i, U_{i+1} are the cumulative drug amounts excreted up to times t, 2t, t_i and $t_i + \Delta t$, respectively. The slopes of the plots of the left-hand sides of Eqns. 4 and 5 vs t and $(2 - \frac{U_{2t}}{U_t})$ will be equal to K and U_∞, respectively. Also, the slope of the line resulting from the plot of $\ln(U_{i+1} - U_i)$ vs t_i equals $-K$ (Eqn. 6), and the intercept of the plot of U_i vs $(U_{i+1} - U_i)$ equals U_∞ (Eqn. 7).

(b) The urinary excretion rate, dU/dt, of unchanged drug for the model is described by Eqn. 8 (Gibaldi and Perrier, 1975):

$$\frac{dU}{dt} = k_e D\, e^{-Kt} \tag{8}$$

where t is midpoint of urine collection period. In Eqn. 8 the term dU/dt is the instantaneous urinary excretion of the drug, but practically, one can only determine the average urinary excretion rate, i.e. $\Delta U/\Delta t$. However, Martin (1967) has shown that, if the urinary excretion rate is determined at equal time intervals, Δt, the ratio of the average rate to the instantaneous rate remains constant, i.e.

$$\lambda = \frac{\Delta U/\Delta t}{dU/dt} \tag{9}$$

and the constant λ is given by:

$$\lambda = \frac{e^{\frac{K\Delta t}{2}} - e^{\frac{-K\Delta t}{2}}}{K \cdot \Delta t} \tag{10}$$

Substitution of $(\Delta U/\Delta t)/\lambda$ for dU/dt into Eqn. 8 yields

$$\frac{\Delta U}{\Delta t} = \lambda k_e D\, e^{-Kt} \tag{11}$$

Eqn. 11 in logarithmic form, i.e.

$$\ln(\Delta U/\Delta t) = \ln(\lambda k_e D) - Kt \tag{12}$$

is used for the estimation of the value of K.

The application of methods of derivations given in a previous report (Barzegar-Jalali, 1981a) to Eqns. 3 and 11 will result in the following graphical equations for estimating U_∞:

$$U_t = U_\infty \left(1 - \frac{(\Delta U/\Delta t)_{2t}}{(\Delta U/\Delta t)_t}\right) \tag{13}$$

$$U_t = U_\infty - \frac{1}{\lambda K}\left(\frac{\Delta U}{\Delta t}\right)_t \tag{14}$$

(c) Eqn. 3 can be written as:

$$U_t = U_\infty - U_\infty\, e^{-Kt} \tag{15}$$

Eqn. 15 is similar to Eqn. 2 given in a previous report (Barzegar-Jalali, 1982) and applying a similar method of derivation used in that report to Eqn. 15 gives:

$$\left(\frac{\int_0^t U \cdot dt}{t}\right) = U_\infty - \frac{1}{K}\left(\frac{U_t}{t}\right) \tag{16}$$

where $\int_0^t U \cdot dt$ is the area under U_t vs t plot between times 0 and t. Eqn. 16 is applicable to any time scheme. The intercept and slope of a plot of the left-hand side of Eqn. 16 vs (U_t/t) will be equal to U_∞ and $-1/K$, respectively.

Once U_∞ and K are known the value of k_e is calculated from Eqn. 17

$$k_e = \frac{KU_\infty}{D} \tag{17}$$

(2) The constant rate intravenous infusion

The cumulative drug amount, U, excreted up to time, t, during the infusion is given by Eqn. 18 (Gibaldi and Perrier, 1975).

$$U = \frac{k_e k_0}{K} \cdot t - \frac{k_e k_0}{K^2} + \frac{k_e k_0}{K^2} \cdot e^{-Kt} \tag{18}$$

where k_0 is the rate of drug infusion, expressed in amount per unit time. The integration of Eqn. 18 between times 0 and t yields:

$$\int_0^t U \cdot dt = \frac{k_e k_0}{2K} \cdot t^2 - \frac{k_e k_0}{K^2} \cdot t - \frac{k_e k_0}{K^3} \cdot e^{-Kt} + \frac{k_e k_0}{K^3} \tag{19}$$

Eqn. 19 is rearranged to give:

$$\int_0^t U \cdot dt = \frac{k_e k_0}{2K} \cdot t^2 - \frac{1}{K}\left[\frac{k_e k_0}{K} \cdot t - \frac{k_e k_0}{K^2} + \frac{k_e k_0}{K^2} \cdot e^{-Kt}\right] \tag{20}$$

But, according to Eqn. 18 the term inside the bracket equals U_t, therefore:

$$\int_0^t U \cdot dt = \frac{k_e k_0}{2K} \cdot t^2 - \frac{U_t}{K} \tag{21}$$

Dividing both sides of Eqn. 21 by t^2 gives:

$$\left(\frac{\int_0^t U \cdot dt}{t^2}\right) = \frac{k_e k_0}{2K} - \frac{1}{K} \cdot \left(\frac{U_t}{t^2}\right) \tag{22}$$

where the integral represents the area under U_t vs t plot between times 0 and t. The intercept, I, and the slope, S, of the line resulting from the plot of $(\int_0^t U \cdot dt/t^2)$ vs (U_t/t^2) will be equal to $k_e k_0/2K$ and $-1/K$, respectively. Therefore, the value of k_e is calculated from Eqn. 23:

$$k_e = \frac{2I}{k_0 S} \tag{23}$$

Other methods of estimating the k_e value from the presteady-state and steady-state data are given by Gibaldi and Perrier (1975). Also, methods of obtaining the parameters of the model from early blood level data have been presented in a previous report (Barzegar-Jalali, 1981b).

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