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Estimation of parameters of linear two-compartment open models with constant intravenous infusion using early blood level data

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In previous reports methods of estimating the parameters of the linear one-compartment open model with a constant rate intravenous infusion from early blood level (Barzegar-Jalali, 1981b) and urinary excretion data (Barzegar-Jalali, 1982a) as well as the advantage of the methods have been discussed. In this communication methods of obtaining the parameters of the linear two-compartment open model with constant intravenous infusion from early blood level data are presented.

(a) The plasma concentration, C, of a drug with a linear two-compartment open model during a constant rate intravenous infusion is given by Eqn. 1:

$$C = C_{ss} - L\,e^{-\alpha t} - M\,e^{-\beta t} \tag{1}$$

where L, M, α and β are constants and their definitions can be found in the textbooks (Gibaldi and Perrier, 1975; Wagner, 1975), and C_{ss} is the steady-state concentration of the drug.

The derivative of Eqn. 1 with respect to time is:

$$dC/dt = \alpha L\,e^{-\alpha t} + \beta M\,e^{-\beta t} \tag{2}$$

Eqn. 2 may be written as Eqn. 3:

$$\dot{C} = L'\,e^{-\alpha t} + M'\,e^{-\beta t} \tag{3}$$

where $\dot{C} = dC/dt$, $L' = \alpha L$, and $M' = \beta M$.

It is obvious from Eqn. 3 that the shape of a plot of ln $\dot{C}$ vs t will be similar to the shape of a plot of ln C vs t of the same drug with bolus intravenous injection. Therefore, the values of L', M', α and β can be estimated using the residual technique (Gibaldi and Perrier, 1975; Wagner, 1975) and the parallel line method (Barzegar-Jalali, 1982b) in similar ways discussed for the bolus intravenous injection.

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After estimation of L', M', α and β, the value of C_{ss} can be calculated from Eqn. 4.

$$C_{ss} = \frac{L'}{\alpha} + \frac{M'}{\beta} \tag{4}$$

Eqn. 4 is obtained by integration of Eqn. 3 between times 0 and ∞ (infinity).

(b) Re-arrangement of Eqn. 1 yields:

$$C_{ss} - C = L\,e^{-\alpha t} + M\,e^{-\beta t} \tag{5}$$

Eqns. 3 and 5 are similar to Eqns. 22 and 38 given in a previous report (Barzegar-Jalali, 1981a). Applying a similar technique of derivation given in that report to Eqns. 3 and 5 will result in the following equation for the estimation of C_{ss} value from the early blood level data:

$$C_{ss} = \frac{C_1(\dot{C}_2\dot{C}_4 - \dot{C}_3^2) - C_2(\dot{C}_1\dot{C}_4 - \dot{C}_2\dot{C}_3) + C_3(\dot{C}_1\dot{C}_3 - \dot{C}_2^2)}{(\dot{C}_2\dot{C}_4 - \dot{C}_3^2) - (\dot{C}_1\dot{C}_4 - \dot{C}_2\dot{C}_3) + (\dot{C}_1\dot{C}_3 - \dot{C}_2^2)} \tag{6}$$

in which C_1, C_2 and C_3 are the blood levels at times t, 2t and 3t; and $\dot{C}_1$, $\dot{C}_2$, $\dot{C}_3$, $\dot{C}_4$ are the values of dC/dt at times t, 2t, 3t and 4t, respectively.

(c) It is evident that at the post-distributive phase Eqns. 2 and 5 will reduce to Eqns. 7 and 8:

$$dC/dt = \beta M\,e^{-\beta t} \tag{7}$$

$$C_{ss} - C = M\,e^{-\beta t} \tag{8}$$

Dividing both sides of Eqn. 8 by Eqn. 7 and simplification and re-arrangement of resulting equation will yield:

$$C = C_{ss} - \frac{dC/dt}{\beta} \tag{9}$$

The intercept of a line resulting from a plot of C vs dC/dt will be equal to C_{ss}.

Once L', M', α and β are known, other parameters of the model can be calculated from the classical equations (Gibaldi and Perrier, 1975; Wagner, 1975).

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