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New approach for graphical analysis of linear two-compartment open models with bolus intravenous injection

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The only available graphical analysis of the linear two-compartment open model with bolus intravenous injection for obtaining the parameters of the model is based on the residual technique (Gibaldi and Perrier, 1975; Wagner, 1975).

In this report a new approach (which may be named the parallel line method) for graphical analysis of the model for estimating its parameters is presented.

The blood level curve for the model is described by:

$$C = A\,e^{-\alpha t} + B\,e^{-\beta t} \tag{1}$$

where C is drug concentration in blood at time t, and e is base for natural logarithm. A, B, α, and β are constants and their definitions can be found in the textbooks (Gibaldi and Perrier, 1975; Wagner, 1975). A plot of the logarithm of the concentration vs time, according to Eqn. 1, will give a bi-exponential curve which will consist of distribution and elimination phases. The constant α (the distribution parameter) is by definition greater than β (the elimination parameter), and therefore, at some time the term $A\,e^{-\alpha t}$ will approach zero while $B\,e^{-\beta t}$ will still have a finite value. Eqn. 1 will then reduce to Eqn. 2

$$C = B\,e^{-\beta t} \tag{2}$$

which in logarithms is:

$$\ln C = \ln B - \beta t \tag{3}$$

Hence, the value of β can be estimated from the slope of the terminal linear phase (the elimination phase) of the plot and the zero time intercept B is obtained by extrapolation of the linear phase to $t = 0$. In the semilogarithmic bi-exponential blood level plot, the equation of a line drawn from a point at the distribution phase

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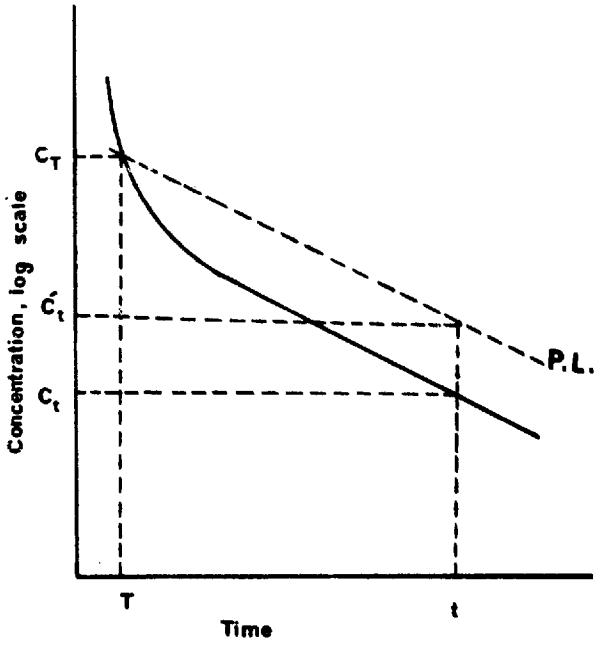

Fig. 1. Semilogarithmic blood level plot of a hypothetical linear two-compartment open model with bolus intravenous injection and the parallel line (P.L.) for presentation of the variables involved in Eqn. 9. See text for the meanings of the symbols.

parallel to the terminal linear phase of the plot (Fig. 1) is:

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

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

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

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

$$C_T = A e^{-\alpha T} + B e^{-\beta T} \tag{6}$$

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

$$C'_t = B e^{-\beta t}\left[1 + \frac{A}{B} e^{-(\alpha-\beta)T}\right] \tag{7}$$

But, according to Eqn. 2 the term $B e^{-\beta t}$ 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

$$C_t' = C_t\left[1 + \frac{A}{B}e^{-(\alpha-\beta)T}\right] \tag{8}$$

Rearranging Eqn. 8 and taking logarithms of both sides of the resulting equation would give Eqn. 9:

$$\ln\left(\frac{C_t'}{C_t} - 1\right) = \ln\left(\frac{A}{B}\right) - (\alpha - \beta)T \tag{9}$$

where C_t and C_t' are calculated from Eqns. 2 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 the chosen t, provided t corresponds to a concentration at the linear and/or extrapolated linear elimination phase.

If the values of the left-hand side of Eqn. 9 were determined for different Ts, then a line could be plotted whose intercept and slope would be equal to $\ln(A/B)$ and $-(\alpha-\beta)$, respectively. Since B and β can be obtained by means of Eqn. 3, therefore, the values of A and α can be readily calculated from the values of the mentioned intercept and slope.

In the cases where only two data points are available at the distribution phase, the parameters A and α are still calculable from two simultaneous equations using Eqn. 9.

Once, A, B, α and β are known, other parameters of the model can be obtained from the classical equations (Gibaldi and Perrier, 1975; Wagner, 1975).

Eqn. 9 was applied to the first 3 blood levels of warfarin given by Wagner (1975). Using the values of B and β calculated by the author, the values of A and α obtained were 29.79 μg/ml and 3.152 h^{-1} which were very close to the values (i.e. 29.99 μg/ml and 3.149 h^{-1}) estimated by the author from the residual technique.

Gibaldi, M. and Perrier, D., In Swarbrick, J. (Ed.), Pharmacokinetics, Marcel Dekker, New York, 1975, Ch. 2.

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