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Some applications of the parallel line method

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The parallel line method has been used for graphical analysis of the one-compartment open model with first-order absorption and elimination rates as well as the linear two-compartment open model with bolus intravenous injection (Barzegar-Jalali, 1982b, 1983). In this report it will be shown that the classical residuals method can be considered as a special case for the parallel line method. Also, some other applications of the method are presented.

(1) The one-compartment open model with first-order absorption and elimination rates

(a) In the semilogarithmic blood level plot, the equation of a line drawn from a point at the early curvature part of the plot parallel to the terminal linear phase is:

$$\ln C_t' - \ln C_T = -K(t - T) \tag{1}$$

where C_t' is a hypothetical concentration on the parallel line at time t, C_T is an experimentally determined drug concentration on the early curvature part of the blood level curve at time T, and K is a first-order elimination rate constant of the drug. Eqn. 1 can be written as Eqn. 2

$$C_t' = C_T e^{-Kt} \cdot e^{KT} \tag{2}$$

The concentration, C_t, corresponding to time t on the terminal linear phase and/or the extrapolated terminal linear phase of the blood level plot is given by Eqn. 3 (Gibaldi and Perrier, 1975)

$$C_t = C_0 \cdot e^{-Kt} \tag{3}$$

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where C_0 is the zero-time intercept. Dividing both sides of Eqn. 3 by 2 gives:

$$\frac{C_t}{C'_t} = \frac{C_0}{C_T \cdot e^{KT}} = \frac{C_0}{C_T} \cdot e^{-KT} \tag{4}$$

or

$$C_T \frac{C_t}{C'_t} = C_0 \cdot e^{-KT} \tag{5}$$

But, the value of C_T is given by Eqn. 6 (Gibaldi and Perrier, 1975)

$$C_T = C_0 \cdot e^{-KT} - C_0 \cdot e^{-k_a T} \tag{6}$$

in which k_a is a first-order absorption rate constant of the drug.

Substitution of the term $C_T \cdot (C_t/C'_t)$ for $C_0 \cdot e^{-KT}$ into Eqn. 6 will yield Eqn. 7

$$C_T\left(\frac{C_t - C'_t}{C'_t}\right) = C_0 \cdot e^{-k_a T} \tag{7}$$

which in logarithms is

$$\ln\left[C_T\left(\frac{C_t - C'_t}{C'_t}\right)\right] = \ln C_0 - k_a T \tag{8}$$

C'_t and C_t are given by Eqns. 2 and 3. The slope of a line resulting from the plot of the left-hand side of Eqn. 8 vs T will be equal to $-k_a$.

When $t = T$, then C'_t and C_t will be equal to C_T and C'_T (a concentration on the extrapolated terminal linear phase of the blood level plot corresponding to time T), respectively. Thus, substitution of C_T and C'_T for C'_t and C_t into Eqn. 8 and simplification will result in Eqn. 9

$$\ln(C'_T - C_T) = \ln C_0 - k_a T \tag{9}$$

which is the equation of the classical residuals method.

(b) In the case where the absorption abruptly ceases, the classical plots for estimating the first-order absorption rate constant will be curved (Leeson and Weintraub, 1973; Wagner, 1974). Also, the parallel line method given above and in a previous report (Barzegar-Jalali, 1983) would give a curved plot for the case. However, if the blood samples are taken according to T,2T scheme, it will be possible to obtain a linear plot from the parallel line method as follows. The equations of the parallel lines for the scheme are:

$$\ln C'_t - \ln C_T = -K(t - T) \tag{10}$$

$$\ln C''_t - \ln C_{2T} = -K(t - 2T) \tag{11}$$

These equations can be written as Eqns. 12 and 13

$$C_t' = C_T \cdot e^{-Kt} \cdot e^{KT} \tag{12}$$

$$C_t'' = C_{2T} \cdot e^{-Kt} \cdot e^{2KT} \tag{13}$$

Substituting the values of C_T and C_{2T} into these equations would yield Eqns. 14 and 15

$$C_t' = \left(C_0 \cdot e^{-KT} - C_0 \cdot e^{-k_aT}\right) \cdot e^{-Kt} \cdot e^{KT} \tag{14}$$

$$C_t'' = \left(C_0 \cdot e^{-2KT} - C_0 \cdot e^{-2k_aT}\right) \cdot e^{-Kt} \cdot e^{2KT} \tag{15}$$

Dividing Eqn. 15 by Eqn. 14, simplification and re-arrangement would give:

$$\frac{C_t''}{C_t'} = \frac{1 - e^{-2(k_a - K)T}}{1 - e^{-(k_a - K)T}} = 1 + e^{-(k_a - K)T} \tag{16}$$

Eqn. 16 may be written as Eqn. 17

$$\ln\left(\frac{C_t'}{C_t'' - C_t'}\right) = (k_a - K)T \tag{17}$$

where C_t' and C_t'' are given by Eqns. 12 and 13. The value of K is obtained from the slope of terminal linear phase of the semilogarithmic blood level plot. The slope of a line resulted from plotting the left-hand side of Eqn. 17 vs T will be equal to $(k_a - K)$ from which k_a can be readily estimated. Eqn. 17 was applied to 0.0833, 0.1666, 0.25, 0.5 and 1 h data points in Table 5 of Wagner's paper (1974). The k_a value obtained was 1.0439 h^{-1} which was very close to the actual value, i.e. 1.0455 h^{-1}.

Other methods of obtaining k_a value for the case have been given by Leeson and Weintraub (1973), Wagner (1974) and Barzegar-Jalali (1981, 1982a).

(2) The linear two-compartment open model with bolus intravenous injection

Applying a similar method of derivation given in (1a) to the model will result in Eqn. 18 which can be used for graphical estimation of the model parameters A and α.

$$\ln\left[C_T\left(\frac{C_t' - C_t}{C_t'}\right)\right] = \ln A - \alpha T \tag{18}$$

in which C_T is an experimentally determined drug level in the early part of the blood level curve at time T, C_t' and C_t being given by $C_T \cdot e^{-(t-T)\beta}$ and $B \cdot e^{-\beta t}$, respectively. The parameters A, B, α and β have their usual meanings.

In the special case where $t = T$, C'_t and C_t are replaced by C_T and C'_T (a hypothetical concentration on the extrapolated linear phase of the blood level plot corresponding to time T), respectively. Thus, Eqn. 18 simplifies to Eqn. 19

$$\ln(C_T - C'_T) = \ln A - \alpha T \tag{19}$$

which is the equation of the residuals method.

(3) The linear 3-compartment open model with bolus intravenous injection

(a) The drug concentration for the model is given by:

$$C_T = L \cdot e^{-\alpha T} + M \cdot e^{-\gamma T} + N \cdot e^{-\beta T} \tag{20}$$

in which L, M, N, α, β and γ are constants and their definitions can be found in textbooks (Gibaldi and Perrier, 1975; Wagner, 1975). The equation (in exponential form) of a line drawn from early curvature part of the blood level plot parallel to the terminal linear β phase of the plot is

$$C'_t = C_T e^{-\beta t} \cdot e^{\beta T} \tag{21}$$

Substituting for C_T from Eqn. 20 into Eqn. 21 gives:

$$C'_t = N \cdot e^{-\beta t}\left[\frac{L}{N} \cdot e^{-(\alpha-\beta)T} + \frac{M}{N} \cdot e^{-(\gamma-\beta)T} + 1\right] \tag{22}$$

The concentration, C_t, on the terminal linear and/or extrapolated terminal linear phase of the blood level plot corresponding to time t is given by

$$C_t = Ne^{-\beta t} \tag{23}$$

Thus, substituting C_t from Eqn. 23 into Eqn. 22 and re-arrangement would yield:

$$\left(\frac{C'_t}{C_t} - 1\right) = \frac{L}{N} \cdot e^{-(\alpha-\beta)T} + \frac{M}{N} \cdot e^{-(\gamma-\beta)T} \tag{24}$$

A semilogarithmic plot of the left-hand side of Eqn. 24 vs T will consist of an early curvature part and a terminal linear phase with the slope of $-(\gamma - \beta)/2.303$ and the zero-time intercept of M/N (assuming $\alpha > \gamma > \beta$) from which the values of γ and M can be estimated. The values of β and N are calculable from the slope and intercept of the terminal linear phase of the blood level plot. Application of the parallel line method to this semilogarithmic plot in a similar way discussed in previous reports (Barzegar-Jalali, 1982b, 1983) will yield the values of L and α.

(b) Dividing Eqn. 23 by Eqn. 21 and subsequent re-arrangement will lead to Eqn. 25

$$C_T \cdot \frac{C_t}{C'_t} = N \cdot e^{-\beta T} \tag{25}$$

Substituting for the term $N \cdot e^{-\beta T}$ from Eqn. 25 into Eqn. 20 and re-arrangement would give:

$$C_T \cdot \left(\frac{C'_t - C_t}{C'_t} \right) = L \cdot e^{-\alpha T} + M \cdot e^{-\gamma T} \tag{26}$$

From terminal linear phase of a semilogarithmic plot of the left-hand side of Eqn. 26 vs T one can obtain the values of γ and M. Further application of the parallel line method to this plot will give the values of α and L.

It is obvious that when $t = T$, Eqn. 26 will simplify to equation of the residuals method.

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