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Short communication

Estimation of asymptotic values of absorption plots from early data points of the plots

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The absorption plots of linear open compartment models are described by the following equation (Wagner, 1975a):

$$\frac{A}{V} = \frac{FD}{V}(1 - e^{-k_a t}) \quad (1)$$

where A is the cumulative drug amount absorbed up to time t, V is the volume of distribution of the drug (in the case of the two-compartment open model, it is the volume of the central compartment, i.e. V_1), F is fraction of dose D absorbed, and k_a is a first-order absorption rate constant. The term FD/V is an asymptotic value of the plots.

The value of A_t/V for the one-compartment model is given by Eqn. 2 (Wagner and Nelson, 1963):

$$\frac{A}{V} = C_t + K\int_0^t C \cdot dt \quad (2)$$

in which C_t is drug concentration in blood at time t, K is a first-order elimination rate constant of the drug, and the integral represents the area under blood level curve between times 0 and t.

The A/V for the two-compartment model is denoted as A_{t_n}/V_1 and its value is estimated from Eqn. 3 (Loo and Riegelman, 1968):

$$A_{t_n}/V_1 = (C_1)_{t_n} + k_{el}\int_0^{t_n} C_1 \cdot dt + (C_2)_{t_n} \quad (3)$$

where $(C_1)_{t_n}$ is the drug concentration in the central compartment (the blood compartment), k_{el} is first-order elimination rate constant of the drug from the central compartment, the integral is the area under blood level curve from time 0 to time t_n, and $(C_2)_{t_n}$ is the amount of drug in the peripheral (the tissue) compartment at time t_n divided by the volume of the central compartment. Loo and Riegelman (1968) have shown that the value of $(C_2)_{t_n}$ could be estimated from Eqn. 4:

$$(C_2)_{t_n} = (C_2)_{t_{n-1}} \cdot e^{-k_{21}\Delta t} + k_{12}/k_{21} \cdot (C_1)_{t_{n-1}}(1 - e^{-k_{21}\Delta t}) + k_{12}\Delta C_1 \cdot \Delta t/2 \quad (4)$$

where $(C_2)_{t_{n-1}}$ and $(C_1)_{t_{n-1}}$ are the values of C_2 and C_1 at time t_{n-1} (i.e. time of previous data point), respectively, k_{12} is a first-order rate constant for transfer of drug from central to peripheral compartment, k_{21} is a first-order rate constant for transfer of drug from peripheral compartment to central compartment, $\Delta t = t_n - t_{n-1}$ and $\Delta C_1 = (C_1)_{t_n} - (C_1)_{t_{n-1}}$.

Eqn. 1 is usually used in the form of Eqn. 5 to construct the sigma-minus plot for the estimation of k_a value:

$$\ln\left(\frac{FD}{V} - \frac{A}{V}\right) = \ln\left(\frac{FD}{V}\right) - k_a t \tag{5}$$

In order to calculate the left-hand side of this equation one has to estimate the maximum or the asymtotic value of A/V (i.e. the value of FD/V). The asymptotic value is calculated either from averaging the terminal values of A/V or from multiplying the elimination rate constant by the total area under the blood level curve (Wagner, 1975b). In the cases where the absorption abruptly ceases the calculation of the asymptotic value by these methods would result in a curved sigma-minus plot (Wagner, 1974). Also, when the time interval for blood sampling becomes long (large Δt value in Eqn. 4) the sigma-minus plot will be curved (Wagner, 1975b). In order to circumvent the problem and to obtain k_a value, Wagner (1974, 1975b) has recommended the use of the Guggenheim method or any alternative method not involving the asymptote.

In this report equations are derived from which the asymptotic value can be estimated from early A/V values. And when the value obtained from the equations is employed, the sigma-minus plots for the cases mentioned above would be linear. Details of the derivation of the equations are as follows.

(a) Using the method of equal time intervals, Wagner (1975a) has derived the following equation from Eqn. 1:

$$\left(\frac{A}{V}\right)_{i+1} - \left(\frac{A}{V}\right)_i = \frac{FD}{V}(1 - e^{-k_a \Delta t})e^{-k_a t_i} \tag{6}$$

where $(A/V)_{i+1}$ and $(A/V)_i$ are the successive values of (A/V) at times $t_i + \Delta t$ and t_i, respectively. According to Eqn. 1 the term $e^{-k_a t_i}$ is given by:

$$e^{-k_a t_i} = \frac{(FD/V) - (A/V)_i}{(FD/V)} \tag{7}$$

Substitution for $e^{-k_a t_i}$ from Eqn. 7 into Eqn. 6 and subsequent rearrangement would yield:

$$\left(\frac{A}{V}\right)_i = \frac{FD}{V} - \frac{1}{1 - e^{-k_a \Delta t}}\left[\left(\frac{A}{V}\right)_{i+1} - \left(\frac{A}{V}\right)_i\right] \tag{8}$$

The intercept of the line resulted from plotting $(A/V)_i$ vs $[(A/V)_{i+1} - (A/V)_i]$ is equal to FD/V.

(b) The values of A/V for the scheme t,2t are given by:

$$\left(\frac{A}{V}\right)_t = \frac{FD}{V}(1 - e^{-k_a t}) \tag{9}$$

$$\left(\frac{A}{V}\right)_{2t} = \frac{FD}{V}(1 - e^{-2k_a t}) \tag{10}$$

Dividing both sides of Eqn. 10 by Eqn. 9 would result in Eqn. 11:

$$\frac{(A/V)_{2t}}{(A/V)_t} = 1 + e^{-k_a t} \tag{11}$$

or

$$\frac{(A/V)_{2t}}{(A/V)_t} - 1 = e^{-k_a t} \tag{12}$$

Substituting $e^{-k_a t}$ from Eqn. 12 into Eqn. 9 gives the following equation:

$$\left(\frac{A}{V}\right)_t = \frac{FD}{V}\left[2 - \frac{(A/V)_{2t}}{(A/V)_t}\right] \tag{13}$$

The slope of the line resulting from the plot of $(A/V)_t$ vs $[2 - (A/V)_{2t}/(A/V)_t]$ would be equal to FD/V.

(c) Taking the derivative of Eqn. 1 with respect to time would yield Eqn. 14 (Wagner, 1975a):

$$\frac{d(A/V)}{dt} = \frac{k_a FD}{V} e^{-k_a t} \tag{14}$$

Eqn. 14 in the logarithmic form, i.e.

$$\ln\left[\frac{d(A/V)}{dt}\right] = \ln\left(\frac{k_a FD}{V}\right) - k_a t \tag{15}$$

can be used for the graphical estimation of a k_a without determining the value of FD/V. In Eqn. 14 the term d(A/V)/dt is the instantaneous rate of change of (A/V) with respect to time, but practically one can only determine the average rate, i.e. Δ(A/V)/Δt. However, application of the technique of derivation given by Martin (1967) to Eqns. 1 and 14 shows that the ratio of the average rate to the instantaneous rate is a constant provided that the values of (A/V) are determined at equal time intervals, Δt, i.e.:

$$\lambda = \frac{\Delta(A/V)/\Delta t}{d(A/V)/dt} \tag{16}$$

and the value of the constant λ is given by:

$$\lambda = \frac{e^{\frac{k_a \Delta t}{2}} - e^{\frac{-k_a \Delta t}{2}}}{k_a \cdot \Delta t} \tag{17}$$

Since λ is a constant, a plot of the $\ln\frac{\Delta(A/V)}{\Delta t}$ vs t (the times at the midpoints of the Δ(A/V)/Δt intervals) would be linear and parallel to a plot of the $\ln\frac{d(A/V)}{dt}$ vs t provided Δt is constant for each point plotted. Consequently, no error will arise in

the calculation of k_a from the slope of the plot if Δt is constant. In the derivation of Eqn. 17 it has been assumed that the trapezoidal areas under the blood level curve were equal to the actual value of the intergrals.

Having borne in mind the considerations mentioned above, the derivative equations for the scheme t,2t can be written as follows:

$$\left[\Delta(A/V)/\Delta t\right]_t = \lambda \frac{k_a FD}{V} e^{-k_a t} \tag{18}$$

$$\left[\Delta(A/V)/\Delta t\right]_{2t} = \lambda \frac{k_a FD}{V} e^{-2k_a t} \tag{19}$$

Division of both sides of Eqn. 19 by Eqn. 18 gives:

$$\frac{\left[\Delta(A/V)/\Delta t\right]_{2t}}{\left[\Delta(A/V)/\Delta t\right]_t} = e^{-k_a t} \tag{20}$$

Substituting for $e^{-k_a t}$ from Eqn. 20 into Eqn. 1 would result in Eqn. 21:

$$\left(\frac{A}{V}\right)_t = \frac{FD}{V}\left\{1 - \frac{\left[\Delta(A/V)/\Delta t\right]_{2t}}{\left[\Delta(A/V)/\Delta t\right]_t}\right\} \tag{21}$$

Eqn. 21 is an equation of a line whose slope equals FD/V.

(d) The following equation is obtained from the rearrangement of Eqn. 18:

$$\frac{V}{\lambda k_a FD}\left[\frac{\Delta(A/V)}{\Delta t}\right]_t = e^{-k_a t} \tag{22}$$

After substitution of $e^{-k_a t}$ from Eqn. 22 into Eqn. 1 and subsequent simplification Eqn. 23 is obtained:

$$\left(\frac{A}{V}\right)_t = \frac{FD}{V} - \frac{1}{\lambda k_a}\left[\frac{\Delta(A/V)}{\Delta t}\right]_t \tag{23}$$

The intercept of the plot of $(A/V)_t$ vs $[\Delta(A/V)/\Delta t]_t$ will be equal to FD/V.

It should be pointed out that in the case where the absorption abruptly ceases, the maximum A/V value estimated from the equations given in this report would be the theoretical value whereas, the terminal method gives the practical value.

When Eqns. 8, 13 and 23 were applied to simulated data given in the Table 5 of the paper of Wagner (1974) the asymptotic values obtained were 99.9, 100.1 and 99.8, respectively, which were essentially equal to the actual value (i.e. 100) given by the author. The value obtained by the terminal method was 70.50 which had resulted in a curved sigma-minus plot.

In the application of Eqns. 8 and 23 the 0.25, 0.5, 0.75 and 1 h data points and for Eqn. 13 the 0.0833, 0.1666, 0.25, 0.5 and 1 h data points were used.

Also Eqns. 8 and 23 were applied to 0.4, 0.8, 1 2, 1.6 and 2 h data points of the Table 3 of a Wagner's paper (1975b), using the set 3 which had resulted in a curved sigma-minus plot. The asymptotes obtained were 100.3 and 100.5, respectively. The actual value was 100. When the obtained values were used in sigma-minus plots, the absorption rate constants were, 0.4954 h^{-1} and 0.4940 h^{-1}, respectively, that were very close to the actual value, i.e. 0.5 h^{-1}.

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