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Short Communications

Calculation of infinity value of cumulative drug amount excreted via urine in bi-exponential processes

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One of the methods of assessing the extent of bioavailability is to determine the total amount of drug excreted in the urine (i.e. infinity value). Several methods for the determination of the infinity value from terminal mono-exponential (linear phase in semilogarithmic plot) of a bi-exponential urinary excretion profile are available, some of which have been reviewed by Newburger et al. (1979). These methods may require collection of urine samples over relatively long periods to ensure the sample being in the terminal mono-exponential phase. For this reason Newburger et al. (1979) have derived an equation which allows infinity values for bi-exponential processes to be predicted in the early non-linear phase when 5 urine samples are taken at equal time intervals. The equation is applicable to both a one-compartment model with first-order absorption and a two-compartment model with bolus intravenous injection.

However, the authors have shown that the equation is very sensitive to the number of decimal places appearing in the data used. In other words, experimental data with different numbers of decimal places may produce a large error in the predicted infinity value.

In this communication two fairly simple equations for the calculation of the infinity value for the two models (i.e. a one-compartment model with first-order absorption and a two-compartment model with bolus intravenous injection) are derived using the early non-linear data. The equations are discussed from the standpoints of accuracy of calculated infinity value, number of urine samples employed, and sensitivity to number of decimal places in data. Details of the derivations are as follows:

(1) The one compartment model with first-order absorption. The urinary excretion rate of a drug, dU/dt, following first-order input into a one-compartment model is given by the following equation (Gibaldi and Perrier, 1975):

$$\frac{dU}{dt} = \frac{k_e k_a FD}{k_a - K} \cdot e^{-Kt} - \frac{k_e k_a FD}{k_a - K} \cdot e^{-k_a t} \qquad (1)$$

where k_e, k_a, and K are first-order rate-constants for urinary excretion, absorption and elimination, respectively. F is fraction of dose D absorbed, and t is the midpoint of the urine collection period. Eqn. 1 can be written as:

$$R = Ax - Ay \qquad (2)$$

where

$$R = \frac{dU}{dt}, \quad A = \frac{k_e k_a FD}{k_a - K}, \quad x = e^{-Kt}, \text{ and } \quad y = e^{-k_a t}.$$

If urinary excretion rates are determined at equal time intervals, then equations for successive rates are as follows:

$$R_1 = Ax - Ay \tag{3}$$

$$R_2 = Ax^2 - Ay^2 \tag{4}$$

$$R_3 = Ax^3 - Ay^3 \tag{5}$$

Dividing both sides of Eqns. 4 and 5 by Eqn. 3 and subsequent simplification will give the following expressions:

$$\frac{R_2}{R_1} = x + y \tag{6}$$

$$\frac{R_3}{R_1} = x^2 + y^2 + xy \tag{7}$$

Eqns. 6 and 7 may be written as:

$$\left(\frac{R_2}{R_1}\right)^2 = (x + y)^2 \tag{8}$$

$$\frac{R_3}{R_1} = (x + y)^2 - xy \tag{9}$$

Subtraction of Eqn. 9 from Eqn. 8 yields:

$$xy = \left(\frac{R_2}{R_1}\right)^2 - \frac{R_3}{R_1} \tag{10}$$

For the one-compartment model with first-order absorption the amount of intact drug remaining to be excreted is given by the following equation (Gibaldi and Perrier, 1975):

$$U_\infty - U = \frac{U_\infty k_a}{k_a - K} \cdot e^{-Kt} - \frac{U_\infty K}{k_a - K} \cdot e^{-k_a t} \tag{11}$$

where U_∞ is the amount of intact drug ultimately excreted in the urine (the infinity value), U is the cumulative amount of intact drug excreted at time t, and k_a and K have been defined previously. Eqn. 11 may be written as Eqn. 12:

$$U_\infty - U = Bx - Ey \tag{12}$$

where

$$B = \frac{U_\infty k_a}{k_a - K}, \quad E = \frac{U_\infty K}{k_a - K}, \quad x = e^{-Kt}, \text{ and } \quad y = e^{-k_a t}.$$

For successive equal time intervals (the times that Rs are determined) the corresponding equations are:

$$U_\infty - U_1 = Bx - Ey \tag{13}$$

$$U_\infty - U_2 = Bx^2 - Ey^2 \tag{14}$$

$$U_\infty - U_3 = Bx^3 - Ey^3 \tag{15}$$

Solving Eqn. 13 for B gives Eqn. 16:

$$B = \frac{U_\infty - U_1 + Ey}{x} \tag{16}$$

Substitution of B from Eqn. 16 into Eqns. 14 and 15 results in the following equations:

$$U_\infty - U_2 = xU_\infty - xU_1 + Exy - Ey^2 \tag{17}$$

$$U_\infty - U_3 = x^2U_\infty - x^2U_1 + Ex^2y - Ey^3 \tag{18}$$

Solving Eqn. 17 for E gives:

$$\frac{U_\infty - U_2 - xU_\infty + xU_1}{y(x - y)} = E \tag{19}$$

Substitution of E from Eqn. 19 into Eqn. 18 and solving the resulting equation for U_∞ yields the following equation:

$$U_\infty = \frac{U_3 + xyU_1 - U_2(x + y)}{1 + xy - (x + y)} \tag{20}$$

Substitution of (x + y) and xy from Eqns. 6 and 10, respectively, into Eqn. 20 gives:

$$U_\infty = \frac{R_1^2U_3 + U_1(R_2^2 - R_1R_3) - U_2R_1R_2}{R_1^2 + R_2^2 - R_1R_3 - R_1R_2} \tag{21}$$

The calculation of U_∞ by Eqn. 21 requires 5 urine samples (including zero time sample). As with the equation of Newburger et al. (1979), Eqn. 21 is independent of the relative value of k_a and K.

(2) The two-compartment model with bolus intravenous injection. The equation describing the urinary excretion rate of a drug, dU/dt, with the two-compartment model after bolus intravenous injection is given by the following equation (Gibaldi and Perrier, 1975):

$$\frac{dU}{dt} = \frac{k'_e D(\alpha - k_{21})}{\alpha - \beta} \cdot e^{-\alpha t} + \frac{k'_e D(k_{21} - \beta)}{\alpha - \beta} \cdot e^{-\beta t} \tag{22}$$

where k'_e = urinary excretion rate-constant, D = intravenous dose, t = midpoint of urine collection period, k_{21} = rate-constant for transfer of the drug from the peripheral compartment to the central compartment, α and β = complex constants composed of the system of microparameters.

Eqn. 22 may be written as:

$$R = Lz + Mv \tag{23}$$

where

$$R = \frac{dU}{dt}, \quad L = \frac{k'_e D(\alpha - k_{21})}{\alpha - \beta}, \quad M = \frac{k'_e D(k_{21} - \beta)}{\alpha - \beta}, \quad z = e^{-\alpha t},$$

and $v = e^{-\beta t}$. Using the method of equal time intervals, the following equations may be written as:

$$R_1 = Lz + Mv \tag{24}$$

$$R_2 = Lz^2 + Mv^2 \tag{25}$$

$$R_3 = Lz^3 + Mv^3 \tag{26}$$

$$R_4 = Lz^4 + Mv^4 \tag{27}$$

Solving Eqn. 24 for L and substitution of the resulting equation for L into Eqns. 25, 26 and 27 would lead to the following Eqns:

$$R_2 = R_1 z - Mvz + Mv^2 \tag{28}$$

$$R_3 = R_1 z^2 - Mvz^2 + Mv^3 \tag{29}$$

$$R_4 = R_1 z^3 - Mvz^3 + Mv^4 \tag{30}$$

Again solving Eqn. 28 for M and substitution of the resulting equation for M into Eqns. 29 and 30 would yield:

$$R_3 = -R_1 vz + R_2(v + z) \tag{31}$$

$$R_4 = -R_1vz(v + z) + R_2(v^2 + z^2 + vz) \tag{32}$$

Eqns. 31 and 32 may be written as:

$$R_3(v + z) = -R_1vz(v + z) + R_2(v + z)^2 \tag{33}$$

$$R_4 = -R_1vz(v + z) + R_2(v + z)^2 - R_2vz \tag{34}$$

Subtraction of Eqn. 34 from Eqn. 33, and then simplification and rearrangement of the resulting equation would yield:

$$R_4 = -R_2vz + R_3(v + z) \tag{35}$$

Solving Eqns. 31 and 35 for the terms (vz) and (v + z) yields:

$$(vz) = \frac{R_2R_4 - R_3^2}{R_1R_3 - R_2^2} \tag{36}$$

$$(v + z) = \frac{R_1R_4 - R_2R_3}{R_1R_3 - R_2^2} \tag{37}$$

The equation describing the amount of unchanged drug remaining to be excreted after bolus intravenous injection of a drug with the two-compartment model is as follows (Gibaldi and Perrier, 1975):

$$U_\infty - U = \frac{U_\infty(k_{10} - \beta)}{\alpha - \beta} \cdot e^{-\alpha t} + \frac{U_\infty(\alpha - k_{10})}{\alpha - \beta} \cdot e^{-\beta t} \tag{38}$$

where U_∞ is the infinity value, U is cumulative drug amount excreted to time t, k_{10} is elimination rate-constant of the drug from the central compartment, and α and β have been defined previously. Eqn. 38 can be written as:

$$U_\infty - U = Nz + Pv \tag{39}$$

where

$$N = \frac{U_\infty(k_{10} - \beta)}{\alpha - \beta}, \quad P = \frac{U_\infty(\alpha - k_{10})}{\alpha - \beta}, \quad z = e^{-\alpha t}, \quad \text{and}$$

$v = e^{-\beta t}$. For successive equal time intervals (the times that Rs were determined), the equations are:

$$U_\infty - U_1 = Nz + Pv \tag{40}$$

$$U_\infty - U_2 = Nz^2 + Pv^2 \tag{41}$$

$$U_\infty - U_3 = Nz^3 + Pv^3 \tag{42}$$

Solving Eqn. 40 for N and substituting the resulting equation for N into Eqns. 41 and 42 would give the following expressions:

$$U_\infty - U_2 = zU_\infty - zU_1 - Pvz + Pv^2 \tag{43}$$

$$U_\infty - U_3 = z^2U_\infty - z^2U_1 - Pvz^2 + Pv^3 \tag{44}$$

Solving Eqn. 43 for P and substituting the resulting equation for P into Eqn. 44 and rearrangement would yield Eqn. 45:

$$U_\infty = \frac{U_3 + U_1vz - U_2(v + z)}{1 + vz - (v + z)} \tag{45}$$

Substitution for the terms (vz) and (v + z) from Eqns. 36 and 37 into Eqn. 45 gives:

$$U_\infty = \frac{U_3(R_1R_3 - R_2^2) + U_1(R_2R_4 - R_3^2) - U_2(R_1R_4 - R_2R_3)}{(R_1R_3 - R_2^2) + (R_2R_4 - R_3^2) - (R_1R_4 - R_2R_3)} \tag{46}$$

Eqn. 46 requires 6 urine samples (including zero time sample) and similar to the equation of Newburger et al. (1979) is independent of the relative value of the rate-constants involved in the process. Applying Eqn. 46 to the first 5 data points (plus zero time data point, i.e. 0) in Table II of the paper of Newburger et al. (1979), a predicted infinity value of 114.2 mg was obtained whereas using their equation, the value calculated by the authors from the same data was 116.5 mg. The experimentally obtained value reported in that paper was 113.9 mg. Eqn. 46 appears to be less sensitive to the number of decimal places in data than the equation of Newburger et al. (1979). Using data given in Table IV of that paper and applying Eqn. 46 to the data and figures with one, two, and three decimal places, the predicted values of 104.63 (4.6% error), 99.78 (0.22% error), and 99.94 (0.06% error) were obtained, respectively. Using the equation of Newburger et al. (1979) the corresponding values were 48.3 (51.7% error), 108.98 (8.98% error), and 99.96 (0.04% error), respectively.

It should be borne in mind that the R values in Eqns. 21 and 46 are actually the instantaneous excretion rate values of drug and that experimentally one can only determine the average rates. However, as Martin (1967) has shown, the shorter the equal time interval for urine collection relative to biological half-life of drug, the closer the average rates to the instantaneous rates.

REFERENCES

Gibaldi, M. and Perrier, D., In Swarbrick, J. (Ed.), Pharmacokinetics, Marcel Dekker, New York, 1975, Chapters 1 and 2.

Martin, B.K., Drug urinary excretion data – some aspects concerning the interpretation. Br. J. Pharmacol. Chemother., 29 (1967) 181–193.

Newburger, J., Wagner, J.G. and Stavchansky, S., A method to predict infinity values for biexponential processes. J. Pharmacokin. Biopharm., 7 (1979) 417–425.