International Journal of Pharmaceutics, 8 (1981) 235–238
Elsevier/North-Holland Biomedical Press

Short Communication

Prediction of infinity value of cumulative drug amount excreted via urine in tri-exponential processes

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Methods for prediction of infinity value of cumulative drug amount excreted via urine in bi-exponential processes have been given by Newburger et al. (1979) and Barzegar-Jalali (1981).

In this report a method of prediction of the infinity value for tri-exponential processes (i.e. two-compartment open model with first-order absorption, distribution and elimination rates and linear 3-compartment open model with bolus intravenous injection) from early non-linear data is given.

The equation describing the urinary excretion rate of drug, dU/dt, for the two models is as follows:

$$\frac{dU}{dt} = L\,e^{-\alpha t} + M\,e^{-\beta t} + N\,e^{-\gamma t} \tag{1}$$

Where L, M, N, α, β and γ are constants, and their definitions for each model can be found in the textbooks (Gibaldi and Perrier, 1975; Wagner, 1975) and t is the midpoint of the urine collection period.

Eqn. 1 may be written as:

$$R = Lx + My + Nz \tag{2}$$

where $R = dU/dt$, $x = e^{-\alpha t}$, $y = e^{-\beta t}$ and $z = e^{-\gamma t}$.

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

$$R_1 = Lx + My + Nz \tag{3}$$

$$R_2 = Lx^2 + My^2 + Nz^2 \tag{4}$$

$$R_3 = Lx^3 + My^3 + Nz^3 \tag{5}$$

$$R_4 = Lx^4 + My^4 + Nz^4 \tag{6}$$

$$R_5 = Lx^5 + My^5 + Nz^5 \tag{7}$$

$$R_6 = Lx^6 + My^6 + Nz^6 \tag{8}$$

Solving Eqn. 3 for N gives Eqn. 9

$$N = \frac{R_1 - Lx - My}{z} \tag{9}$$

Substitution for N from Eqn. 9 into Eqns. 4 through 8 will result in the following equations:

$$R_2 = Lx^2 + My^2 + R_1z - Lxz - Myz \tag{10}$$

$$R_3 = Lx^3 + My^3 + R_1z^2 - Lxz^2 - Myz^2 \tag{11}$$

$$R_4 = Lx^4 + My^4 + R_1z^3 - Lxz^3 - Myz^3 \tag{12}$$

$$R_5 = Lx^5 + My^5 + R_1z^4 - Lxz^4 - Myz^4 \tag{13}$$

$$R_6 = Lx^6 + My^6 + R_1z^5 - Lxz^5 - Myz^5 \tag{14}$$

Solving Eqn. 10 for M and substitution of the resulting equation for M into Eqns. 11 through 14 will yield:

$$R_3 = Lx(x - y)(x - z) + R_2y - R_1yz + R_2z \tag{15}$$

$$R_4 = Lx(x - y)(x - z)(x + y + z) + R_2y^2 - R_1y^2z + R_2z^2 + R_2zy - R_1z^2y \tag{16}$$

$$R_5 = Lx(x - y)(x - z)(x^2 + y^2 + z^2 + xy + xz + zy) + R_2y^3 - R_1zy^3 + R_2z^2y - R_1z^3y + R_2zy^2 - R_1z^2y^2 + R_2z^3 \tag{17}$$

$$R_6 = Lx(x - y)(x - z)(x^3 + y^3 + z^3 + xz^2 + x^2z + xy^2 + zy^2 + x^2y + yz^2 + xyz) + R_2y^4 - R_1zy^4 + R_2zy^3 - R_1z^2y^3 + R_2y^2z^2 - R_1y^2z^3 + R_2yz^3 - R_1yz^4 + R_2z^4 \tag{18}$$

After solving Eqn. 15 for L and substitution of the resulting equation for L into Eqns. 16 through 18 the following equations are obtained:

$$R_4 = R_3(x + y + z) - R_2(xy + xz + zy) + R_1xyz \tag{19}$$

$$R_5 = R_3(x^2 + y^2 + z^2 + xy + xz + zy) - R_2(x^2y + x^2z + y^2z + yz^2 + xy^2 + xz^2 + 2\,xyz) + R_1(x^2yz + xy^2z + xyz^2) \tag{20}$$

$$R_6 = R_3(x^3 + y^3 + z^3 + xz^2 + x^2z + xy^2 + zy^2 + x^2y + yz^2 + xyz) - R_2(x^3y + x^3z + y^3x + y^3z + z^3x + z^3y + x^2y^2 + x^2z^2 + y^2z^2 + 2x^2yz + 2xy^2z + 2xyz^2) + R_1(x^3yz + xy^3z + xyz^3 + x^2y^2z + x^2yz^2 + xy^2z^2) \tag{21}$$

Multiplying both sides of Eqn. 19 by the term (x + y + z), subtraction of the resulting equation from Eqn. 20, and subsequent simplification and rearrangement would give Eqn. 22.

$$R_5 = R_4(x + y + z) - R_3(xy + xz + yz) + R_2xyz \tag{22}$$

Multiplication of both sides of Eqn. 20 by the term (x + y + z), subtraction of the resulting equation from Eqn. 21 and rearrangement would yield:

$$R_6 = R_5(x + y + z) - (xy + xz + yz)[R_3(x + y + z) - R_2(xy + xz + yz) + R_1xyz] + R_3xyz \tag{23}$$

But the term inside the bracket equals R_4 (according to Eqn. 19). Therefore:

$$R_6 = R_5(x + y + z) - R_4(xy + xz + yz) + R_3xyz \tag{24}$$

Solving Eqns. 19, 22 and 24 by the determinant rule for the terms (x + y + z), (xy + xz + yz) and (xyz) would result in the following expressions:

$$(x + y + z) = \frac{R_4(R_2R_4 - R_3^2) - R_5(R_1R_4 - R_2R_3) + R_6(R_1R_3 - R_2^2)}{R_3(R_2R_4 - R_3^2) - R_4(R_1R_4 - R_2R_3) + R_5(R_1R_3 - R_2^2)} \tag{25}$$

$$(xy + xz + yz) = \frac{R_3(R_3R_5 - R_2R_6) - R_4(R_3R_4 - R_1R_6) + R_5(R_2R_4 - R_1R_5)}{R_3(R_2R_4 - R_3^2) - R_4(R_1R_4 - R_2R_3) + R_5(R_1R_3 - R_2^2)} \tag{26}$$

$$(xyz) = \frac{R_3(R_4R_5 - R_3R_6) - R_4(R_4^2 - R_2R_6) + R_5(R_3R_4 - R_2R_5)}{R_3(R_2R_4 - R_3^2) - R_4(R_1R_4 - R_2R_3) + R_5(R_1R_3 - R_2^2)} \tag{27}$$

The equation describing the amount of unchanged drug remaining to be excreted for the two models is:

$$U_\infty - U = L'x + M'y + N'z \tag{28}$$

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, L′, M′ and N′ are constants, and x, y and z have been defined previously.

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

$$U_\infty - U_1 = L'x + M'y + N'z \tag{29}$$

$$U_\infty - U_2 = L'x^2 + M'y^2 + N'z^2 \tag{30}$$

$$U_\infty - U_3 = L'x^3 + M'y^3 + N'z^3 \tag{31}$$

$$U_\infty - U_4 = L'x^4 + M'y^4 + N'z^4 \tag{32}$$

Solving Eqn. 29 for N′ and substitution of the resulting equation for N′ into Eqns. 30 through 32 would give the following equations:

$$U_\infty - U_2 = L'x^2 + U_\infty z - U_1z - L'xz + M'y(y - z) \tag{33}$$

$$U_\infty - U_3 = L'x^3 + U_\infty z^2 - U_1z^2 - L'xz^2 + M'y(y^2 - z^2) \tag{34}$$

$$U_\infty - U_4 = L'x^4 + U_\infty z^3 - U_1z^3 - L'xz^3 + M'y(y^3 - z^3) \tag{35}$$

After solution of Eqn. 33 for M′ and substitution of the resulting equation for M′ into Eqns. 34 and 35 would yield:

$$U_\infty - U_3 = L'x(x-y)(x-z) + U_\infty y - U_2 y - U_\infty yz + U_1 yz + U_\infty z - U_2 z \tag{36}$$

$$U_\infty - U_4 = L'x(x-y)(x-z)(x+y+z) + U_\infty y^2 - U_2 y^2 - U_\infty y^2 z + U_1 y^2 z + U_\infty z^2 - U_2 z^2 + U_\infty yz - U_2 yz - U_\infty yz^2 + U_1 yz^2 \tag{37}$$

Solving Eqn. 36 for L′ and substituting the resulting equation for L′ into Eqn. 37 and rearrangement would give Eqn. 38

$$U_\infty = \frac{U_4 - U_3(x+y+z) + U_2(xy+xz+yz) - U_1 xyz}{1 - (x+y+z) + (xy+xz+yz) - xyz} \tag{38}$$

Substitution for the terms (x + y + z), (xy + xz + yz) and (xyz) from Eqns. 25, 26 and 27, respectively, into Eqn. 38 gives:

$$U_\infty = \frac{U_4[R_3(R_2R_4 - R_3^2) - R_4(R_1R_4 - R_2R_3) + R_5(R_1R_3 - R_2^2)]}{[R_3(R_2R_4 - R_3^2) - R_4(R_1R_4 - R_2R_3) + R_5(R_1R_3 - R_2^2)]} - \frac{U_3[R_4(R_2R_4 - R_3^2) - R_5(R_1R_4 - R_2R_3) + R_6(R_1R_3 - R_2^2)]}{[R_4(R_2R_4 - R_3^2) - R_5(R_1R_4 - R_2R_3) + R_6(R_1R_3 - R_2^2)]} + \frac{U_2[R_3(R_3R_5 - R_2R_6) - R_4(R_3R_4 - R_1R_6) + R_5(R_2R_4 - R_1R_5)]}{[R_3(R_3R_5 - R_2R_6) - R_4(R_3R_4 - R_1R_6) + R_5(R_2R_4 - R_1R_5)]} - \frac{U_1[R_3(R_4R_5 - R_3R_6) - R_4(R_4^2 - R_2R_6) + R_5(R_3R_4 - R_2R_5)]}{[R_3(R_4R_5 - R_3R_6) - R_4(R_4^2 - R_2R_6) + R_5(R_3R_4 - R_2R_5)]} \tag{39}$$

Eqn. 39 requires 8 urine samples (including zero time sample) and is independent of the relative value of the rate constants involved in the processes.

In the application of Eqn. 39 to the experimental data one should bear in mind the critical points discussed in previous reports (Newburger et al., 1979; Barzegar-Jalali, 1981).

ACKNOWLEDGEMENT

The author thanks Dr. M. Toomanian of the Mathematics Department, Tabriz University, for helpful discussions.

REFERENCES

Barzegar-Jalali, M., Calculation of infinity value of cumulative drug amount excreted via urine in bi-exponential processes. Int. J. Pharm. (1981) in press.

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

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

Wagner, J.G., Fundamentals of Clinical Pharmacokinetics. Drug Intelligence Publications, Hamilton, Ill., 1975, Ch. 2.