Developments in the Concentration Ratio Method

To the Editor:

Recently, Patel[1] proposed the concentration ratio method (CRM) for determining the unique rate constant, K, of the linear one-compartment open model with equal first-order processes. According to this method, when this model is identified a priori, an overall estimate of K can be obtained by:

$$K = \frac{1}{n-1} \sum_{i=2}^{n} \frac{\ln (t_n/t_{n-1}) - \ln (C_p^n/C_p^{n-1})}{t_n - t_{n-1}} \quad (1)$$

where t_{n-1} and t_n are any two consecutive times while C_p^{n-1} and C_p^n are the corresponding plasma drug concentrations. The purpose of this report is to reveal new features of the CRM which improve its performance.

In deriving eq. 1, Patel postulated the plasma concentrations C_p^{n-1} and C_p^n at any two consecutive times t_{n-1} and t_n. However, this consideration is not necessary since the fundamental equation of the CRM (eq. 5 in Patel's paper) is also valid for any two pairs of data (C_p^x, t_x), (C_p^y, t_y) chosen at random, disregarding the order of the selection. Thus, eq. 5 of Patel's paper can be more generally written as:

$$K = \frac{\ln (t_x/t_y) - \ln (C_p^x/C_p^y)}{t_x - t_y} \quad (2)$$

Relying on the last equation and applying an identical syllogism to that used by Patel to derive eq. 1, it can be seen that the overall estimate of K can be obtained from:

$$K = \frac{2}{n(n-1)} \sum_{i=2}^{n} \frac{\ln (t_x/t_y) - \ln (C_p^x/C_p^y)}{t_x - t_y} \quad (3)$$

This equation gives the estimate for K as an average of combinations of n data points taken two at a time. Inspection of eqs. 1 and 3 shows that the latter is superior to the former since it has $(n - 1)(n - 2)/2$ more solutions for a given number of n data points. This feature is of special importance when a limited number of data are available. For example, if six data points have been collected, eqs. 1 and 3 utilize 5 and 15 solutions for the estimate of K, respectively.

Another point which requires mentioning is that eq. 2 can be rearranged to:

$$\ln \left(\frac{t_x C_p^y}{t_y C_p^x}\right) = K(t_x - t_y) = K\Delta t \quad (4)$$

where Δt is the time interval from t_x to t_y. This equation shows that a plot of $\ln (t_x C_p^y/t_y C_p^x)$ versus Δt gives a straight line with a slope of K. Thus, K can be estimated by simple linear regression when the model is identified a priori.

References and Notes

1. Patel, I. H. *J. Pharm. Sci.* **1984**, *73*, 859.

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