Estimation of Rate Constants for Absorption and Elimination from Blood Concentration Data

Sir:

Wagner (1) discussed estimation of the rate constant for elimination from the slope of the descending part of an apparently linear semilogarithmic plot of concentration of drug in blood plasma against time. He pointed out that such a graphical estimate may be lower than the true value of the rate constant. Also, since the estimate of the absorption rate constant depends upon the value of the elimination rate constant, the estimated value of the absorption rate constant may be in error too. It is the purpose of this communication to show that this difficulty may be overcome by methods of digital computation, although Krüger-Thiemer and Eriksen (2) recently reported that it could not. The problem with the data of Krüger-Thiemer and Eriksen (2) was that blood samples were not taken long enough following oral administration.

Several examples were presented by Wagner (3, 4). One example (4) was the fitting of serum concentrations of tetracycline hydrochloride activity observed in a subject following a single oral dose of a capsule of tetracycline HCl[1] 250 mg. The semilogarithmic plot gave an estimate of 0.130 hr.$^{-1}$ for the elimination rate constant. The residuals, plotted semilogarithmically, gave an estimate of 0.810 hr.$^{-1}$ for the absorption rate constant. Use of these preliminary estimates with an iterative digital computer program gave a least squares fit (using equal weights) with a 57.6% reduction in variance; the rate constant for elimination changed to 0.149 hr.$^{-1}$ and the rate constant for absorption changed to 0.716 hr.$^{-1}$. If one assumes the least squares estimates are the "best" values, then the graphical estimate of the absorption rate constant was 13.1% higher, and the graphical estimate of the elimination rate constant was 12.8% lower than the "best" value, respectively. The latter is of the same order of magnitude as in the simulation example of Wagner (1).

Another example is the fitting of average serum concentrations of erythromycin activity observed in a panel of 12 adult male volunteers following oral administration of 500 mg. of erythromycin activity in tablet form. Preliminary graphical estimation, shown in Fig. 1, gave an estimate of 0.899 hr.$^{-1}$ for the absorption rate constant, 0.393 hr.$^{-1}$ for the elimination rate constant, and 0.58 hr. for the lag time. An iterative digital computer program gave a least squares fit (with weighting according to the reciprocal of the average serum concentrations) with a 73.2% reduction in variance; the absorption rate constant changed to 0.708 hr.$^{-1}$, the elimination rate constant changed to 0.444 hr.$^{-1}$, and the lag time changed to 0.602 hr. If one assumes the least squares estimates are the "best" values, then the graphical estimate of the absorption rate constant was 27.0% higher and the graphical estimate of the elimination rate constant was 11.5% lower than the "best" value, respectively. The least squares fit is shown in Fig. 2.

These two examples are representative of a more general phenomenon. Least squares fitting of all observed serum or plasma concentrations of a set almost always results in an increase of 10 to 15% in the magnitude of the elimination rate constant and a decrease in the magnitude of the absorption rate constant compared with estimates obtained graphically using semilogarithmic paper. This implies that, in such cases, the trend line of the terminal data points of the semilogarithmic plot is slightly curved and not linear as one assumes when estimating the elimination rate constant by the graphical method. This is illustrated by Fig. 3, in which the least squares curve is drawn through the data points on semilogarithmic paper.

This underestimation of the elimination rate constant can be anticipated from the equation for plasma or serum concentration, namely:

$$\text{concn.} = (\text{constant})\,(e^{-k_2 t} - e^{k_1 t}) \quad \text{(Eq. 1)}$$

where $k_1 > k_2$. The observations of concentration underestimate $e^{-k_2 t}$ by the amount $e^{-k_1 t}$; this bias is greater for smaller values of t. A line drawn through the terminal points of a semilogarithmic plot of concentration against time will have successively greater bias to the left. This bias causes the line to have a smaller slope than it should have, thus underestimating k_2, the elimination rate constant.

We have assumed in the above discussion that the smallest rate constant estimated is the elimination rate constant and the larger rate constant is the absorption rate constant. This is usually the case but, in rare instances, the assignments could be reversed. We also assume that the estimate of the smallest rate constant by least squares fitting of all the data points is a more valid estimate than the estimate obtained

[1] Marketed as Panmycin Hydrochloride by The Upjohn Co., Kalamazoo, Mich.

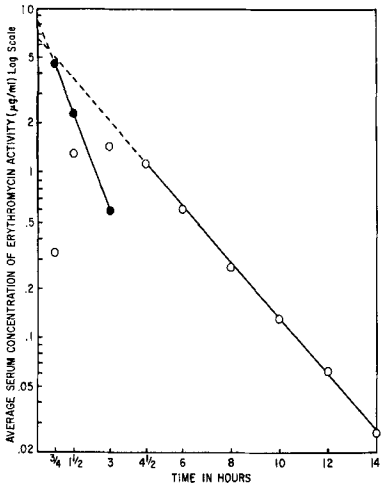

Fig. 1—Illustrates graphical estimation of the rate constants. The terminal linear segment gave an estimate of 0.393 hr.$^{-1}$ for the elimination rate constant. The residuals gave an estimate of 0.899 hr.$^{-1}$ for the absorption rate constant. The intersection of the two lines gave an estimate of 0.58 hr. for the lag time. Key: ○, observed; ●, residuals.

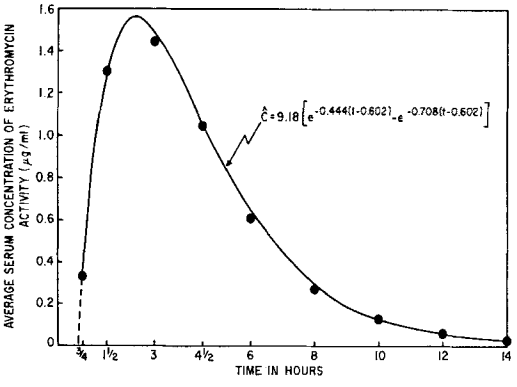

Fig. 2—The black circles are the observed average serum concentrations of erythromycin. The line was drawn by substituting values of time into the equation shown on the figure. The equation was the result of least squares fitting of the observed serum concentrations with a digital computer. Weighting was according to the reciprocals of the average serum concentrations.

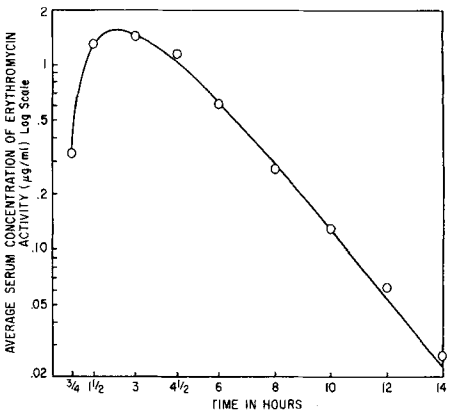

Fig. 3—The circles are the observed average serum concentrations of erythromycin. The line drawn through the points was obtained by substituting values of time into the equation shown on Fig. 2. It should be noted that the line drawn through the terminal six points is slightly curved compared with the straight line in Fig. 1.

graphically from only some of the points. Since most estimates of elimination rate constants reported in the literature were obtained by the latter method, we believe the reported rate constants are lower than the "best" values, and the corresponding half-lives are higher than the "best" values.

(1) Wagner, J. G., *J. Pharm. Sci.*, **52**, 1097(1963).
(2) Krüger-Thiemer, E., and Eriksen, S. P., *ibid.*, **55**, 1249(1966).
(3) Wagner, J. G., *Can. J. Pharm. Sci.*, **1**, 55(1966).
(4) Wagner, J. G., *Clin. Pharmacol. Therap.*, **8**, 201(1967).

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