Maintenance-Dose Prediction Based on a Single Determination of Concentration: Dose of Parent Drug Required to Give a Desired Steady-State Concentration of Metabolite

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Abstract □ A method for predicting the maintenance dose of parent drug required to give a desired steady-state concentration of metabolite, using a single determination of metabolite concentration in serum following the first dose of parent drug, is described. Clinical evidence that such a method is feasible for the drug–metabolite pair imipramine–desipramine has been reported. The error inherent in an estimation of maintenance dose based on a single determination of metabolite concentration is a function of sampling time and the first-order elimination rate constants for parent drug and metabolite (K and k_m, respectively). The method is applicable to drug–metabolite pairs in general by selecting the sampling time (t^*) to give minimum error: $t^* = 1/\bar{k}_m + 1.3/\bar{K}$, when $\bar{k}_m \leq \bar{K}$, and $t^* = 1/\bar{K} + 1.3/\bar{k}_m$, when $\bar{k}_m > \bar{K}$ (bars denote population mean value). The error expected to be encountered in the application of the method to specific drug–metabolite pairs can be analyzed by the graphical methods described.

Keyphrases □ Imipramine—steady-state concentration of desipramine in serum, maintenance dose, single-point prediction method, pharmacokinetics □ Desipramine—steady-state concentration in serum with imipramine administration, maintenance dose, single-point prediction method, pharmacokinetics □ Pharmacokinetics—single-point prediction method for desired steady-state concentration, maintenance dose, drug–metabolite pairs

The use of a single determination of drug concentration in serum at some time after the initial dose to predict the maintenance dose required to give a desired steady-state concentration has become quite popular since Cooper *et al.* (1, 2) first reported its use for lithium in 1973. The method has been applied to drugs with long half-lives [nortriptyline (3–5) and imipramine (6)] as well as drugs with short half-lives [chloramphenicol (7, 8) and theophylline (7, 9)]. A theoretical basis for such a relationship has been described, showing that the method is capable of giving accurate estimates of the maintenance dose needed if the sample is obtained at the appropriate time (10). The error of the method was shown to be a function of the elimination rate constant for the drug in the individual patient. It was later shown that the optimum sampling time (t^*) was equal to $1/\bar{K}$, where $\bar{K}$ is the mean value of the elimination rate constant for parent drug in the population (11).

There have been two instances in which data suggest that the single-point method can be used to predict the maintenance dose of parent drug to give a desired steady-state concentration of metabolite following administration of the parent drug: chloramphenicol following dosing with the succinate ester (7, 8) and desipramine following dosing with the parent drug imipramine (6). In the first case, the optimal sampling time for predicting the maintenance dose was found to be 6 hr, corresponding to the inverse of the mean metabolite elimination rate constant ($1/\bar{k}_m$). In the second case, that of imipramine–desipramine, no optimal sampling time was presented; a good correlation ($r = 0.92$) was noted between the logarithm of the steady-state desipramine concentration and the logarithm of the desipramine concentration obtained 24 hr after a single dose of imipramine. In the imipramine–desipramine case, $1/\bar{k}_m$ would indicate an optimal sampling time of 33 hr. Prediction on the basis of imipramine elimination would suggest a sampling time of 13 hr.

The strength of the correlation between the concentration determined in a single serum sample obtained 24 hr after the first dose and the eventual steady-state concentration of desipramine following administration of imipramine, and the demonstrated success of single-point dose prediction with chloramphenicol suggested that a theoretical framework could be developed to predict the dose of parent drug necessary to achieve a desired concentration of metabolite at steady-state. This report describes the framework and uses it to examine the error inherent in the method, under optimal conditions.

THEORETICAL

The development of an equation relating the maintenance dose of parent drug (D_m) needed to obtain a desired steady-state concentration of metabolite ($C_{ss,m}$) to the concentration of metabolite in serum (C^*_m) at time t^* after administration of an initial dose of parent drug (D^*) proceeds in much the same manner as previously described for parent drug maintenance-dose prediction (10, 11). For simplicity, the kinetics of all species are assumed to conform to linear one-compartment behavior; intravenous injection of the parent drug is also assumed. The general scheme for the elimination of drug is given in Scheme I. Under these conditions, the concentration of metabolite at a specific time after administration of the parent drug is given by:

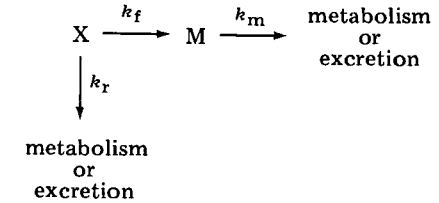
$$C^*_m = \frac{k_f D^*}{V_m(K - k_m)}(e^{-k_m t^*} - e^{-K t^*}) \qquad \text{(Eq. 1)}$$

where V_m is the apparent volume of distribution of the metabolite and K and k_m are the elimination rate constants for parent drug and metabolite, respectively.

The average concentration of metabolite at steady state is:

$$\bar{C}_{ss,m} = \frac{k_f D_m}{K V_m k_m \tau} \qquad \text{(Eq. 2)}$$

where k_f is the formation rate constant of metabolite from parent drug



Scheme I—Model for single-point dose prediction. Key: (X) parent drug; (M) metabolite; (k) first-order rate constant; (subscript r) remainder; (subscript f) formation; (subscript m) metabolite.

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and τ is the dosing interval. The ratio $\overline{C}_{ss,m}/C^*_m$ is therefore:

$$\frac{\overline{C}_{ss,m}}{C^*_m} = \frac{D_m(K - k_m)}{Kk_m\tau D^*(e^{-k_m t^*} - e^{-Kt^*})} \quad \text{(Eq. 3)}$$

The relationship between the maintenance dose and the single concentration determined after the initial dose is:

$$\frac{1}{D_m} = \left[\frac{K - k_m}{\overline{C}_{ss,m}D^*\tau Kk_m(e^{-k_m t^*} - e^{-Kt^*})}\right] C^*_m \quad \text{(Eq. 4)}$$

The term in brackets can be represented by a proportionality factor, Ψ_m:

$$\frac{1}{D_m} = \Psi_m C^*_m \quad \text{(Eq. 5)}$$

where:

$$\Psi_m = \frac{K - k_m}{\overline{C}_{ss,m}D^*\tau Kk_m(e^{-k_m t^*} - e^{-Kt^*})} \quad \text{(Eq. 6)}$$

It should be realized that Ψ_m varies among individuals only as a function of K and k_m; $\overline{C}_{ss,m}$, D^*, t^*, and τ are chosen and held constant for all individuals. The proportionality factor, Ψ_m, is independent of the fraction of dose metabolized to the metabolite of interest (or to other metabolites) and the formation rate constant of the metabolite. The rate constants K and k_m might be more appropriately written as the ratio of clearance to volume of distribution, but the rate constants are written because clearance and volume of distribution do not appear in Ψ_m except as the ratio, K or k_m. This has been addressed in greater detail in the case of single-point parent drug maintenance-dose prediction (11). Since the maintenance dose is determined for an average steady-state concentration, it can be varied if the dosing rate (D_m/τ) is kept constant.

When $K \gg k_m$, as in the case of a prodrug, Ψ_m as defined in Eq. 6 reduces to:

$$\Psi_{m,K\gg km} = \frac{e^{k_m t^*}}{\overline{C}_{ss,m}D^*\tau k_m} \quad \text{(Eq. 7)}$$

which more appropriately defines the proportionality factor Ψ previously described for the metabolite chloramphenicol of the prodrug chloramphenicol succinate. When parameter values are substituted, $\Psi_m = \Psi$ as previously defined (10). It is also of interest to note the definition of Ψ_m at the opposite extreme, namely where $k_m \gg K$:

$$\Psi_{m,km\gg K} = \frac{e^{Kt^*}}{\overline{C}_{ss,m}D^*\tau K} \quad \text{(Eq. 8)}$$

As described previously for parent drug (10), Eq. 5 will serve to predict accurate values of D_m when Ψ_m remains reasonably constant throughout the population. Thus, t^* must be chosen in such a manner to result in minimum variability of Ψ_m as a function of K and k_m. This, by definition, will be the optimum value of t^*. When the sample is obtained at the optimum t^*, a population average value of Ψ_m will have the best chance of working for maintenance-dose prediction purposes.

Figure 1 shows how t^* can be chosen such that Ψ_m is kept reasonably constant as K and k_m vary through the population. Ranges of K and k_m approximate population values for imipramine–desipramine (6). In this figure $\Psi_m/\overline{\Psi}_m$ is plotted to allow direct comparison between the plots. $\overline{\Psi}_m$ is the average value of Ψ_m throughout the population. Also, the lowest values of the axes are at the far right corner in each plot; this departure from convention is made to afford the clearest view of the surface. Among the three values of t^* examined the optimum value of t^* (to the nearest hour) is 48 hr (Fig. 1b) where the plot of $\Psi_m/\overline{\Psi}_m$ is relatively flat compared to t^* = 36 hr (Fig. 1a) and t^* = 60 hr (Fig. 1c). In this case, the maximum error is an ~25% overprediction of dose at low values of k_m in combination with low values of K.

Figure 1 also shows that the greatest error of the method is encountered at the extremes of the values of K and k_m[1]. As the range of values considered here is exceeded, the error will increase (see below). However, if a Gaussian distribution of these rate constants is assumed, it is evident that a very small fraction of the population will be represented by these extreme values. Thus, the method can be expected to work well for a very large majority of the population.

Optimization of Sampling Time—The optimum time for obtaining the sample for maintenance-dose prediction can be determined by constructing plots such as those in Fig. 1 and selecting as t^* the sampling time

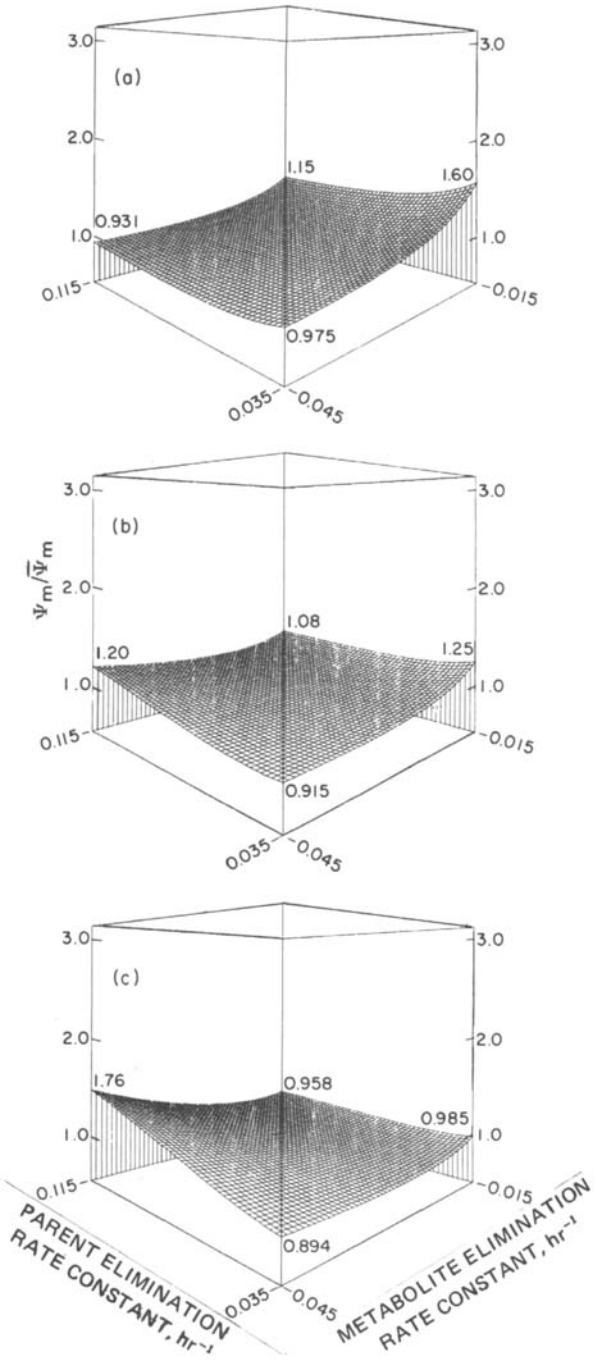

Figure 1—*Relationships between $\Psi_m/\overline{\Psi}_m$ and the elimination rate constants for metabolite (k_m) and parent drug (K) for the parent drug–metabolite pair imipramine–desipramine at t* = 36 (a), 48 (b), and 60 hr (c). The optimum value of t*, 48 hr, gives the most nearly planar surface. The lowest values of all axes appear at the far right corner of each figure.*

which gives the least variability in $\Psi_m/\overline{\Psi}_m$ as a function of K and k_m. This is rather cumbersome and time consuming because of the need for accurate three-dimensional plotting capability.

The problem can be simplified to two dimensions. Ψ_m is a ratio, and the variables K and k_m appear in both the numerator and denominator. For Ψ_m to be constant throughout a population, the numerator and denominator must change in proportion to one another since K and k_m assume different values from one individual to another. A plot of the numerator of Ψ_m (Eq. 6) *versus* its denominator should be as nearly linear as possible at the optimum choice of t^*. Since the value of Ψ_m varies among individuals as a function of K and k_m only, $D^*\tau\overline{C}_{ss,m}$ can be assigned a value of 1 for the purpose of sampling time optimization.

Figure 2 shows such plots for the case of imipramine–desipramine.

[1] In Fig. 1, error is reflected by the degree of curvature of the surface. If there was no inherent error, every individual would have the same value of Ψ_m and $\Psi_m/\overline{\Psi}_m$ would equal 1 at all combinations of K and k_m. As the surface becomes more curved, error increases.

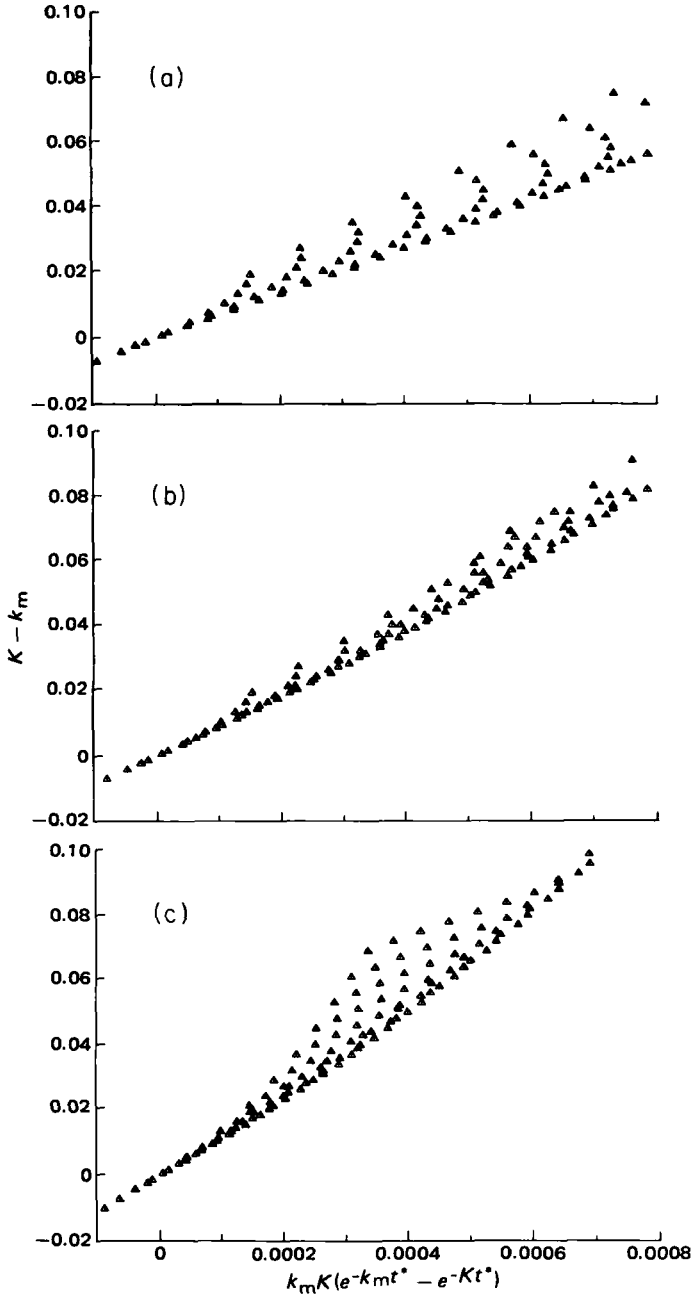

Figure 2—*Plots of the numerator of Eq. 6* versus *the denominator for the parent drug–metabolite pair imipramine–desipramine at* t* = *36 (a), 48 (b), and 60 hr (c). The optimum value of* t* *has the minimum scatter of points, which can be judged numerically as described in the text. This plot represents an alternative optimization method to Fig. 1.*

Points are chosen in this plot by selecting values of K and k_m in nested loops at fixed intervals; plots a, b, and c in Fig. 2 correspond to the respective three-dimensional plots in Fig. 1. The plots in Fig. 2 take the form of scatter plots because of the complex nature of the variability of the numerator and denominator of Ψ_m as a function of K and k_m. Figure 2 shows minimum scatter for $t^* = 48$ hr (Fig. 2b); more scatter is evident for $t^* = 36$ and 60 hr in Fig. 2a and c, respectively. Thus, the outcome of optimization schemes shown in Figs. 1 and 2 is the same.

It is not necessary to rely on a visual comparison of plots to select optimum values of t^* for a given set of values of K and k_m. Since a plot of the numerator of Eq. 6 *versus* the denominator will have a slope equal to Ψ_m, the optimum t^* will result in minimum scatter about a regression line. Measures of relative goodness of fit can therefore be used for optimization purposes. This method has been used for the case of imipramine–desipramine, and 48 hr was again obtained for the optimum value of t^*. Agreement was verified to an accuracy of 1 hr. The coefficients of

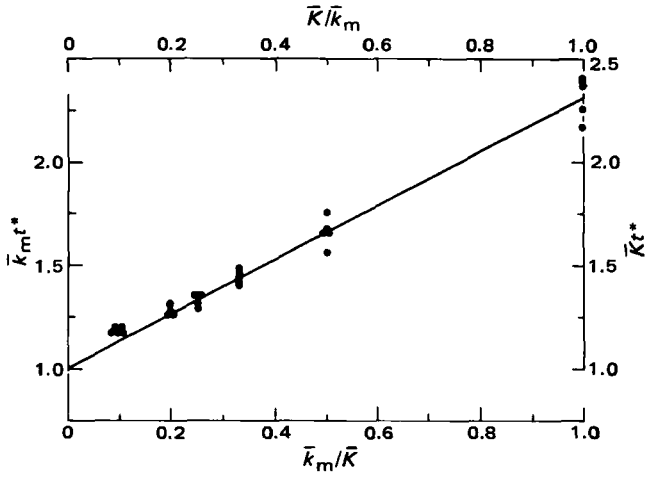

Figure 3—*Relationship between optimum* t* *and the ratio of mean elimination rate constant values. If* $\bar{K} > \bar{k}_m$, *read* $\bar{k}_m$t* *from the left axis from the point on the line corresponding to the appropriate value of the ratio* $\bar{k}_m/\bar{K}$; *if* $\bar{k}_m > \bar{K}$, *read* $\bar{K}$t* *corresponding to the value of the ratio* $\bar{K}/\bar{k}_m$ *from the axis on the right. Equation of line:* $y = 1 + 1.3x$.

variation of the slopes of the plots in Fig. 2 (as %) are 24.7, 12.7, and 22.2 for $t^* = 36$, 48, and 60 hr, respectively.

In the case of maintenance-dose prediction for the parent drug, it was possible to arrive at a simple calculation for the optimum value of t^*; *i.e.*, $t^* = 1/K$ where K is the population mean elimination rate constant for the parent drug. The case of maintenance dose of parent drug to give a desired metabolite concentration at steady state is analytically somewhat more complex. However, using either of the techniques described above, a general solution can be obtained.

In the course of these investigations, we determined the optimum value of t^* for a number of combinations of K and $\bar{k}_m$ (bars denote mean). It was apparent that as the ratio of $\bar{k}_m/K$ increased, the optimum value of t^* increased. Previous experience indicated that a plot of optimum t^* as a function of the ratio $\bar{k}_m/K$ would not be linear and its slope at any point would be a function of the absolute values of $\bar{k}_m$ and K. We therefore constructed a plot of $\bar{k}_m t^*$ as a function of the ratio $\bar{k}_m/K$ and found it to be linear and to serve for predictive purposes whenever $K \geq \bar{k}_m$. A plot of this empirical relationship is shown in Fig. 3. The points in the plot represent the results of optimizations using the technique described above for various ranges of K and k_m. In this figure, t^* could be calculated by reading the value of $\bar{k}_m t^*$ of the left vertical axis for a given value of $\bar{k}_m/K$ when $K \geq k_m$. Conversely, when $k_m > K$, $\bar{K}t^*$ can be read off the plot corresponding to a given value of $\bar{K}/\bar{k}_m$. Thus, given the population mean value of K and k_m, the optimum value of t^* can be estimated from the regression coefficients of Fig. 3. For $\bar{K} \geq \bar{k}_m$:

$$\bar{k}_m t^* = 1 + 1.3\bar{k}_m/\bar{K} \qquad \text{(Eq. 9)}$$

or

$$t^* = \frac{1}{\bar{k}_m} + \frac{1.3}{\bar{K}} \qquad \text{(Eq. 10)}$$

and when $\bar{k}_m > \bar{K}$:

$$\bar{K}t^* = 1 + 1.3\bar{K}/\bar{k}_m \qquad \text{(Eq. 11)}$$

or

$$t^* = \frac{1}{\bar{K}} + \frac{1.3}{\bar{k}_m} \qquad \text{(Eq. 12)}$$

In the case of a prodrug, $K \gg k_m$ and Eq. 9 becomes $t^* \simeq 1/\bar{k}_m$, which is the clinical observation with chloramphenicol when the prodrug, chloramphenicol succinate, is given (8).

The slope of the line in Fig. 3 varies slightly with the range of rate constant values encountered for a particular drug–metabolite pair; *i.e.*, the optimum value of t^* is slightly affected by the range of K and k_m encountered. Figure 4, where $\bar{k}_m/\bar{K} = 0.5$, shows this effect. t^* (44 hr) is optimized for a fourfold variability in K and k_m and is 4 hr too long for a threefold range and 1 hr too early for a fivefold range. Such an effect has been noted by others when considering t^* in the case of parent drug (12). In Figure 5, where $\bar{k}_m/\bar{K} = 0.1$, this effect is not evident. Thus, use of Fig. 3 or Eqs. 9–12 gives an approximate value for optimum t^*; other

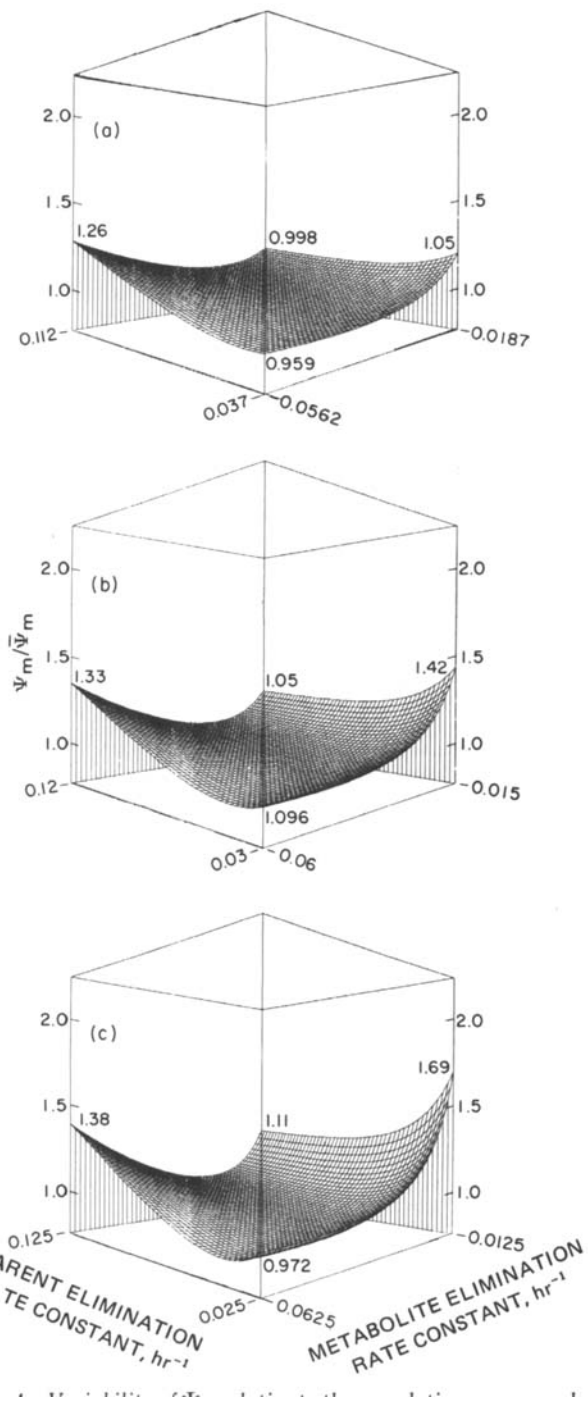

Figure 4—*Variability of Ψ_m relative to the population average value, $\bar{\Psi}_m$, as the range of* K *and* k_m *increases, $\bar{k}_m/\bar{K}$ = 0.5. Range of rate constant values for* k_m *and* K*: (a) threefold; (b) fourfold; (c) fivefold. The lowest values of all axes appear at the far right corner of each figure.*

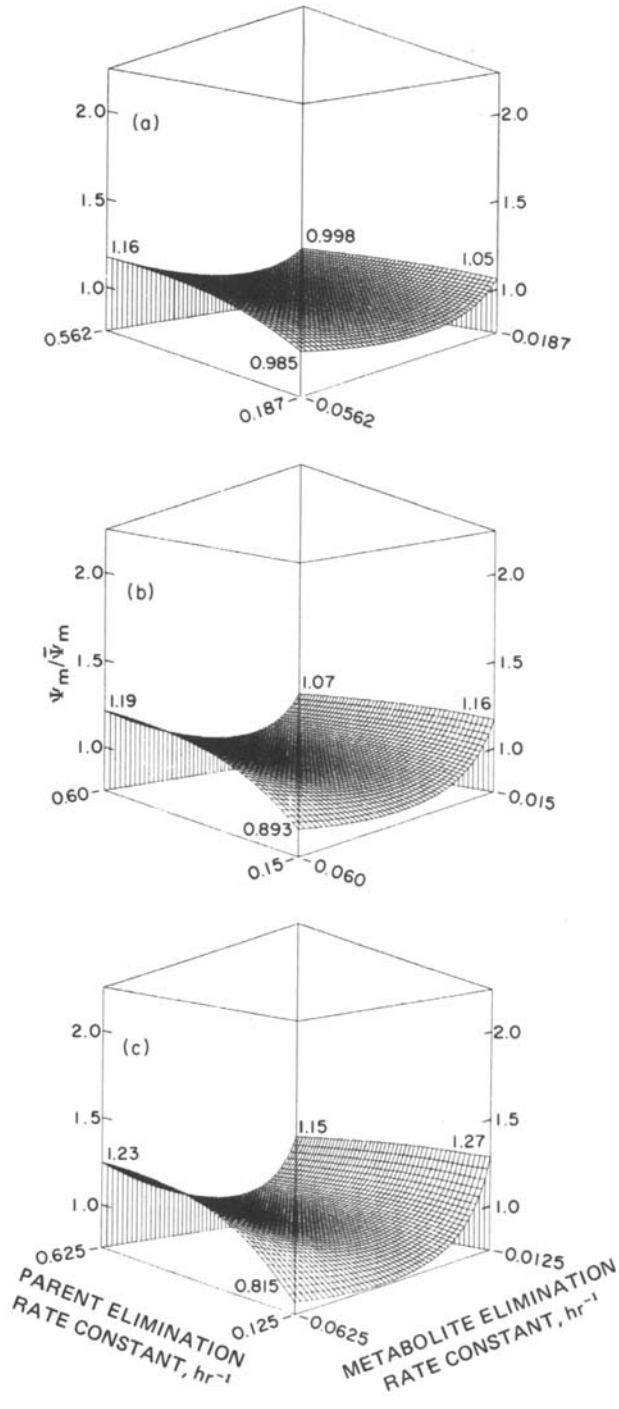

Figure 5—*Variability of Ψ_m relative to the population average value, $\bar{\Psi}_m$, as the range of* K *and* k_m *increases, $\bar{k}_m/\bar{K}$ = 0.1. Range of rate constant values for* k_m *and* K*: (a) threefold; (b) fourfold; (c) fivefold. The lowest values of all axes appear at the far right corner of each figure.*

methods would give more accurate results. Figure 3 and Eqs. 9–12 will give a quick indication as to the possibility of choosing a clinically convenient or feasible sampling time for a particular drug–metabolite pair.

Analysis of Error—Although the optimum value of t^* can be read directly from Fig. 3 or calculated from Eqs. 9–12, that information does not give any insight into the *error* of the method. A direct indication of the magnitude and source of inherent error is obtained from the three-dimensional plots of the type used for optimization in Fig. 1.

These plots for arbitrary cases are presented in Figs. 4 and 5 for cases with $\bar{k}_m/\bar{K}$ = 0.5 and $\bar{k}_m/\bar{K}$ = 0.1, respectively. Actual values of the rate constants cover ranges of three-, four-, and fivefold, respectively, in plots a, b, and c of both figures. Error is greatest as the extreme values of K and k_m are approached in Fig. 4, where the ranges of the two elimination rate constants overlap. Accordingly, as the range is increased, the maximum error increases from 27% at threefold to 69% at fivefold. These errors would result in an overprediction of maintenance dose of the same magnitude.

In Fig. 5 ($\bar{k}_m/\bar{K}$ = 0.1), the ranges of K and k_m do not overlap and at large values of K, the error in maintenance-dose prediction is a function of k_m only and independent of K, as required by Eq. 7. As in Fig. 4, error increases as the range of K and k_m increases, but as the ratio of $\bar{k}_m/\bar{K}$ decreases, the error of the method decreases and is less sensitive to increases in the range of elimination rate constant values.

Neither of these figures gives an indication of the role of the distribution of values of the elimination rate constants in the population. If the

distribution was assumed to be Gaussian, a small fraction of the population would be represented by the values of elimination rate constants at the extreme of the range. Very few individuals would be subjected to the maximum error of the method. Figs. 4 and 5 represent error patterns of specific cases for certain values of K and k_m; they have not been constructed to represent general cases. For any given case, similar plots should be constructed to evaluate error.

DISCUSSION

The optimum sampling time for determining the maintenance dose of parent drug required to give a desired steady-state concentration of metabolite for the drug–metabolite pair imipramine–desipramine indicated by this analysis is 48 hr. A linear relationship between the log of the 24-hr concentration of desipramine following the first dose of imipramine and the log of the eventual steady-state concentration of the drug, if the same dose is kept constant and administered daily, has been found clinically (6). The mathematical basis for relating these two concentrations arises from a rearrangement of Eq. 6 that gives rise to a proportionality factor with the general behavior of Ψ_m (10). The results of the present analysis suggest that the relationship between concentration at 24 hr and eventual steady-state concentration would be curvilinear. A log–log transformation might linearize such a plot. It is expected that a sample collected 48 hr after the first dose would appear to be linearly related to the eventual steady-state concentration.

There are two critical considerations in applying this method to any drug–metabolite pair: (*a*) the error which will be encountered as a function of the elimination kinetics of the pair and (*b*) the possibility that the elimination kinetics may dictate a value of t^* that is not clinically feasible. The variability of Ψ_m is a function of the elimination kinetics of the pair in the population and cannot be overcome when single-point prediction schemes are used. Thus, a poor estimate of maintenance dose will always be obtained for some fraction of the population. When the optimum value of t^* is not used because it is too short to be clinically convenient and a longer time is adopted, the error of the method increases but in a somewhat conservative manner. Patients who eliminate the drug and metabolite slowly will tend to be underdosed and those who eliminate the drug quickly (requiring a relatively larger maintenance dose) tend to be overdosed. This situation is perhaps more tolerable than the converse: when a t^* shorter than the optimum is adopted, patients who eliminate the drug most slowly will tend to be overdosed and those who eliminate it more quickly will tend to be underdosed. Another observation may be more to the point: when the optimum value of t^* is not used, the relationship between $1/D_m$ and C^*_m will become less well-characterized by a straight line. If the curvilinear nature of the relationship can be taken into account, reasonably accurate dose prediction may still be possible.

Single-point dose prediction methods appear to be applicable to most drugs and their metabolites. However, the optimum sampling time for the dose required to give a desired steady-state concentration of the parent drug may be quite different than that required to give a target metabolite concentration. If dosage prediction is warranted for a particular drug (10) and the kinetics of the drug are linear, it appears likely that a single-point method could be developed to suit using the techniques described here. However, it must be remembered that the predicted dose is an estimate that must be confirmed by obtaining samples at steady state.

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Bayesian Approach to Bioequivalence Assessment: An Example

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Abstract □ The statistical methods required for a Bayesian analysis of bioequivalence are outlined and numerically illustrated. The analysis consists of the calculation of the posterior probability, given the experimental results, that the ratio of true means of a new and a standard formulation of a drug with respect to some biological response lies in a given interval. Nomograms helpful for the calculation of these probabilities are provided.

Keyphrases □ Bioequivalence—assessment by Bayesian analysis, statistical methods, example and nomograms □ Bayesian analysis—bioequivalence assessment, statistical methods, example, and nomograms

Comparative bioavailability studies serve to investigate the pharmaceutical properties of two or more formulations of the same drug. Decisions on whether two formulations are bioequivalent are usually made by comparing biological responses such as area under the plasma concentration curve or the maximum peak concentration. Since in many instances the objective of a bioavailability study is not to show a difference between formulations, but rather to investigate whether any difference is of practical importance, Westlake (1) and Metzler (2) suggest that hypothesis tests of no difference are of little value.

In this paper the statistical methods needed to perform a Bayesian analysis of bioequivalence given by Mandallaz and Mau (3) are outlined. This method has been illustrated

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