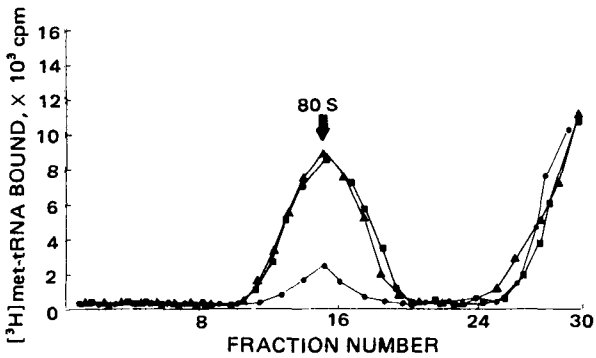

Figure 5b—*Addition of puromycin. Effect of genkwadaphnin and yuanhuacine on the methionyl puromycin reaction of P-388 lymphocytic leukemia lysate (n = 5). Key: (●) control plus puromycin; (▲) genkwadaphnin; (■) yuanhuacine plus puromycin.*

[³H]methionine from the 80 S complex (Fig. 5b). The diterpene esters did not interfere with the formation of a stable 80 S initiation complex but rather inhibited the puromycin release of labeled methionine from the polysome.

These data indicate that I and II similarly block peptide bond formation during elongation peptide chain synthesis. The concentration of drug to block peptide transferase activity was consistent with concentrations required to inhibit whole cell protein synthesis *in vitro*.

The daphnane diterpene esters did not have any significant effects on the individual steps leading to the formation of a stable 80 S initiation complex. The daphnane diterpene esters significantly inhibited both the polyuridine-directed polyphenylalanine synthesis and the formation of the first peptide bond between puromycin and the met-tRNA bound to the 80 S initiation complex. These data strongly indicate that the diterpene esters are potent inhibitors of the peptidyl transferase reaction of the elongation process of protein synthesis of P-388 lymphocytic leukemia cells.

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Bayesian Individualization of Pharmacokinetics: Simple Implementation and Comparison with Non-Bayesian Methods

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Abstract □ One may attempt to individualize drug dosage by estimating an individual's pharmacokinetic parameters. Information useful for this purpose consists of certain population pharmacokinetic parameters (notably those describing the typical relationship between dosage and drug concentrations) and also measured drug concentrations from the individual of concern. Both types of information should be used. A (Bayesian) method that does so has been described in the pharmacokinetic literature. In this report an implementation of the Bayesian method that is readily adapted to a microcomputer is presented. Using simulated data it is compared with two other methods proposed by others, for estimating individual theophylline clearances. Both previously suggested methods are shown to be less precise than the Bayesian method: their typical error magnitudes are 20–70% larger.

Keyphrases □ Bayesian method—individualization of pharmacokinetics, simple implementation and comparison with non-Bayesian methods, theophylline □ Pharmacokinetics—Bayesian individualization, simple implementation and comparison with non-Bayesian methods, theophylline □ Theophylline—Bayesian individualization of pharmacokinetics, simple implementation and comparison with non-Bayesian methods

A great deal of attention has been given to the problem of estimating the pharmacokinetic parameters of individual patients in order to optimize dosage choices. Initially, most attention has been directed at obtaining estimates of individual parameters from the population information relating kinetics to certain patient features (sex, age, renal function, *etc*). More recently, considerable attention has been directed at the estimation of parameters using measured drug levels (1–4).

One particular method, the Bayesian method (3), is intuitively appealing. It involves a continuously changing view of the patient. Before any drug levels are measured,

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the patient is regarded as a typical member of the population of all similar patients with respect to pharmacokinetic parameter values. Once considerable drug level information has become available, the patient is regarded as a unique individual whose pharmacokinetic parameters are distinct from other patients. The point of view is continuously shifted from the first one to the second one as drug level information accumulates.

In this report, a method for implementing the Bayesian approach is outlined that involves only a simple modification of any standard nonlinear least-squares fitting procedure (see *Appendix*). Then, using simulated data, the Bayesian method is compared with two other methods for estimating individual theophylline clearances.

THEORETICAL

Implementation—The basic model used here for the observations of an individual is:

$$y_i = f(P,X_i) + \epsilon_i \qquad \text{(Eq. 1)}$$

where y_i is the ith drug level, $P = (p_1,p_2,\ldots p_s)$ is the vector of the s pharmacokinetic parameters of the model for the individual, X_i is the vector of independent variables (such as time, dose) associated with y_i, and ϵ_i is statistical error that includes measurement error and random intraindividual kinetic variability over time.

The errors, ϵ_i, are assumed to be independent, with zero mean and common variance, σ^2, assumed known. The vector of individual parameters, P, is regarded as arising randomly from a population of such vectors (one for each individual of the population). For each $1 \leq k \leq s$, the population mean and variance of the p_k are the known quantities, θ_k and ω_k^2, respectively. They are obtained presumably from a population study of the drug in question. The assumption allowing for the simplicity of the implementation to be described is that the p_k are pairwise uncorrelated in the population. For convenience, θ will denote the vector $(\theta_1,\theta_2,\ldots\theta_s)$ and Ω will denote the vector $(\omega_1^2,\omega_2^2,\ldots\omega_s^2)$.

When faced with y_i, $i = 1, n$ observations of drug levels, the usual approach is to estimate P using ordinary least squares (OLS). The ordinary least-squares estimate of P, $\hat{P}_{OLS}$, is that value of P minimizing the ordinary least-squares objective function:

$$O_{\text{OLS}}(P) = \sum_{i=1}^{n} (y_i - \hat{y}_i)^2 \qquad \text{(Eq. 2)}$$

where

$$\hat{y}_i = f(P,X_i) \qquad \text{(Eq. 3)}$$

We shall call the $\hat{y}_i$ prediction functions.

The ordinary least-squares estimate minimizes the squared errors between the observations and the prediction functions. Call these squared errors of the first kind.

If the only observations available for estimating P were those of y_i, $\hat{P}_{\text{OLS}}$ would be a natural estimate. However, there are other available observations—the elements of θ, obtained from the population study of the drug. Define $\eta = \theta - P$ to be the vector of differences between the population mean parameters (θ) and each individual's parameters (P). Then, for each k:

$$\theta_k = p_k + \eta_k \qquad \text{(Eq. 4)}$$

Just as Eq. 1 says that the drug level observations (y_i) are equal to prediction functions $f(P,X_i)$, themselves functions of the unknown individual parameters (P) plus a random error (ϵ_i) with known variance (σ^2), so Eq. 4 says that the population observations (θ_k) are equal to prediction functions (p_k) trivial functions of P, plus a random error (η_k) with known variance (ω_k^2). Therefore, the estimate of P should attempt to minimize the squared errors between these population observations and their prediction functions, as well as those of the first kind.

When faced with observations having different error variances, it is customary to estimate parameters using weighted least-squares (WLS). The weighted least squares estimate of P,$\hat{P}_{\text{WLS}}$, is that value of P minimizing

$$O_{\text{WLS}}(P) = \sum_{i=1}^{n} \frac{(y_i - \hat{y}_i)^2}{\sigma^2} + \sum_{k=1}^{s} \frac{(\theta_k - p_k)^2}{\omega_k^2} \qquad \text{(Eq. 5)}$$

Statistical theory states that with different error variances, weighted least-squares estimates are more efficient (and possibly less biased) than ordinary least-squares estimates.

The same estimator ($\hat{P}_{\text{WLS}}$) can be as justified as a Bayesian estimator when a somewhat different line of argument is pursued (3). The authors prefer, therefore, to call the set of parameter values that minimize the expression (5) the Bayesian estimates. The weighted least-squares justification, however, leads directly to a simple practical implementation of the method. The implementation requires only a slight modification of any standard nonlinear weighted least-squares fitting algorithm. The details are presented in the *Appendix* to this paper. The essence of the method is straightforward: the list of data (y_i, $i = 1, n$) is lengthened to include the additional values of $\theta_1,\ldots\theta_s$. The weights for y_i, $i = 1, n$ are set to $1/\sigma^2$, and those for the additional s observations are set to $1/\omega_k^2$, $k = 1, s$. Finally, the user-supplied subroutine that computes and returns $\hat{y}_i$ (required by all nonlinear least-squares programs) is modified to return the current estimate of p_k when called upon to predict the kth additional observation.

A slight modification of the basic approach (see *Appendix*) deals with the special case of uncertain dosage. It may sometimes happen that there is uncertainty about the prior dose history (perhaps because the patient was an outpatient) but that an initial drug level is available so that the dose history for all subsequent levels is known (perhaps because the patient became an inpatient). It may then be preferable to initialize to the first level as suggested in a previous approach (1), to be discussed further in *Examples*. To accommodate this case in the Bayesian approach, a revised model is written that treats the true unknown initial level as another unknown parameter (p_{s+1}) and predicts observations as a function of time and dosage only after that level (see *Examples*). Logically, however, the (measured) initial level may deviate from its true value (p_{s+1}) as much as any other measured level deviates from its predicted value. To allow this, the variance of the error between the observed initial level and p_{s+1} is given by $\omega_{s+1}^2 = \sigma^2$.

Examples—Two examples of common clinical pharmacokinetic situations, the estimation problem for each of which has been approached by other workers, are presented in detail here. The Bayesian method is compared with those other methods using simulated data.

The following are some aspects common to both. The drug used for illustration in both cases is theophylline. The basic pharmacokinetic model for its disposition is the one-compartment model. This model, when used only for intravenous doses has two parameters, volume of distribution (Vd) and clearance (Cl). An initial level, if present in the model, constitutes a third parameter. A reparameterization is used; the new parameters are $p_1 = \log Vd$, $p_2 = \log Cl$, and p_3 = initial level. Logs of Vd and Cl are used because choosing a symmetrical population distribution for them (*e.g.*, the normal) imparts a skewed distribution to Vd and Cl, which accords well with actual experience.

The data used to test the various approaches were simulated. For each example, one hundred pairs of individual clearance (Cl) and volume of distribution (Vd) values were chosen at random. The parameters, p_1 and p_2 for each case, were chosen randomly from normal distributions with means of θ_1 = log (0.5 liters/kg), θ_2 = log (0.052 liters/kg/hr), respectively, (5, 6). The standard deviation of the distribution of the log of a random quantity is approximately equal to the coefficient of variation of the quantity itself. The standard deviations (coefficients of variation of Vd and Cl) used in simulating p_1 and p_2 values were ω_1 = 32% for p_1 and ω_2 = 44% for p_2 (6). Every choice of p_1 and p_2 gave rise to a choice of Vd and Cl by exponentiation. The simulated Vd and Cl values were substituted into pharmacokinetic equations to obtain simulated true drug levels. Random normally distributed errors (ϵ) were then added to these true levels to arrive at simulated observed levels. The ϵ were chosen to have mean zero and standard deviations equal to 1 mg/liter (corresponding to a coefficient of variation of 10% at a typical concentration of 10 mg/liter). The random numbers needed for the simulations were obtained using standard methods (7, 8).

Two estimation methods are applied in each example: the Bayesian method and one of the alternative methods proposed by others and described below. In both examples only clearance is estimated. Each method is used to estimate the clearance of each of the 100 simulated patients, using whatever population parameters the method may entail and the simulated drug level(s). The Bayesian method proceeds by a numerically minimizing expression (5). On the other hand, the alternative methods estimate clearance from the available data using simple direct formulas. The estimate of clearance by any method is denoted $\hat{Cl}$.

The Bayesian method depends on population parameters (standard deviations, ω_1 and ω_2) not used by the other methods. The Bayesian method naturally behaves best when it is provided with the standard

Table I—Performance of Clearance Estimation Methods

Method	$\frac{\omega_{Cl}}{\sigma}$[a]	$\frac{\omega_{Vd}}{\sigma}$[a]	Mean Clearance Error (±*SEM*) as Percent of Mean Clearance: Error, Example 1	Error, Example 2	Absolute Error, Example 1	Absolute Error, Example 2
Alternative	—	—	−5.77(5.8)	−2.82(3.3)	37.1(4.5)	26.4(2.1)
Bayesian	1	1	−1.02(3.0)	−1.08(3.1)	22.2(2.0)[b]	21.7(2.2)[b]
	3/2	1	−4.94(3.4)	−3.77(3.0)	25.6(2.3)[b]	23.1(2.1)[b]
	2/3	1	5.02(3.2)	2.52(3.4)	23.7(2.2)[b]	23.5(2.4)
	1	3/2	0.44(3.0)	−0.26(3.1)	22.5(2.1)[b]	21.4(2.2)[b]
	1	2/3	−0.76(3.0)	−1.56(3.1)	22.5(1.9)[b]	21.7(2.2)[b]

[a] Ratio of standard deviation of clearance (or Vd) to σ used in the Bayesian method. All ratios are divided by the correct ratio so that a value of unity signifies that the correct ratio itself was used. [b] Mean absolute error of Bayesian method less than that of alternative ($p < 0.05$).

deviations actually used to simulate the data. To test its robustness, the Bayesian method was applied five times: once with the true (simulation) standard deviations, once with the ratio of ω_1 to σ assumed to be 3/2 times its true value, once with the ratio assumed to be 2/3 times its true value, and once each for the same changes in the assumed ratio of ω_2 to σ.

To assess the absolute and relative performance of the estimation methods the differences may be examined between estimates of clearances and their true (simulation) values. For each estimation method, the mean error, defined as the mean of the differences between the true clearances and the estimated values, measures the bias of the method. The mean absolute error, defined as the mean of the absolute values of the errors, can be used to measure precision. The relative precision of two methods can be assessed using a paired t-test on the paired absolute errors (*i.e.*, on the value of the absolute error of the first method minus that of the second method). If the mean difference is significantly greater than (less than) zero, the first method is less (more) precise than the second method. It remains only to explain how $f(P,X_i)$ is computed for the Bayesian method, and for the alternative methods, how $\hat{Cl}$ is computed. These definitions follow.

Example 1—A method has been proposed (2) to estimate the maintenance dose required to achieve a target plasma concentration of drug. This method uses the observation of a single drug level after a test dose of drug. Since the maintenance dose must be proportional to individual clearance, the proposal amounts to a method to estimate individual clearance from a single drug level measurement. The appropriate pharmacokinetic model for the single true drug level is:

$$f(P,X) = W = \frac{d}{t_1 Cl}[1 - \exp(-kt_1)]\exp(-k(t_2 - t_1)) \quad \text{(Eq. 6)}$$

where the subscript i has been suppressed, d is the size of the test dose [according to the previous suggestion (2), taken to be 5 mg/kg], t_1 is the duration of the test infusion (0.5 hrs), t_2 is the sampling time for the drug level (6 hr), and k is the ratio of Cl to Vd. The simulated observed level, y, is equal to W plus a randomly chosen value for ϵ.

Using the relationship suggested previously (2), and adjusting its constants so that it estimates clearance, rather than maintenance dose, this method becomes:

$$Cl = 0.266\exp(-0.311\,y) \quad \text{(Eq. 7)}$$

Example 2—A method has been proposed (1) for estimating individual theophylline clearance using one drug level measured shortly after a maintenance infusion has begun (and perhaps shortly after a loading infusion has terminated) and another level measured some hours later. Two drug levels are used, but the first one is regarded as an initial level so that prior dosage may be regarded as unknown. Since both levels are assumed to be measured, errors in both of them must be simulated. Accordingly, the appropriate pharmacokinetic model for the first true drug level is:

$$f(P,X_1) = W_1 = \frac{d}{Vd}\exp(-kt_1) + \frac{R}{Cl}[1 - \exp(-kt_1)] \quad \text{(Eq. 8)}$$

where, for convenience, the initial loading dose, d (5.6 mg/kg), is assumed to be given by an infusion rapid enough so that its contribution to the level measured at time t_1 (2 hr later) may be predicted by a bolus-dose model; R is the maintenance infusion rate, set equal to 0.52 mg/kg/hr so as to result in a typical steady-state concentration of 10 mg/liter; and k is Cl/Vd.

The second true level is modeled as:

$$f(P,X_2) = W_2 = W_1\exp(-kt_2) + \frac{R}{Cl}[1 - \exp(-kt_2)] \quad \text{(Eq. 9)}$$

where t_2 is the time at which y_2 is sampled, measured as the time since t_1. This time is varied randomly from patient to patient according to a normal distribution with a mean of 5 hr, and a standard deviation of 2 hr (but values <3 hr were discarded). These sampling times are in accordance with previous suggestions (1) for sampling times. (Note that for the Bayesian method, the third parameter to be estimated is simply W_1, the true first level.) The simulated observed levels, y_1 and y_2, are obtained from W_1 and W_2 by adding randomly chosen errors ϵ_1 and ϵ_2, respectively.

Clearance is predicted (1) from:

$$\hat{Cl} = \frac{2R}{(y_1 + y_2)} + \frac{2\exp(\theta_1)(y_1 - y_2)}{t_2(y_1 + y_2)} \quad \text{(Eq. 10)}$$

Note that a single population parameter, θ_1, is used here.

RESULTS

Both examples can be discussed together, since the results are quite similar.

Table I presents the performance of the Bayesian and alternative estimation methods for both examples. In Table I, the mean (estimation) error and absolute error for clearance, and their standard errors, are expressed as percentages of the (approximate) population mean clearance, 0.052 liter/hr/kg. The performance of the Bayesian method is shown for all five cases tested: the case in which the method was supplied with the correct ratios of the ω's to σ and the four cases in which incorrect ratios were used. None of the Bayesian performances nor those of the alternative methods exhibited substantial bias (*i.e.*, mean errors were relatively small and in all cases were within two standard errors of zero).

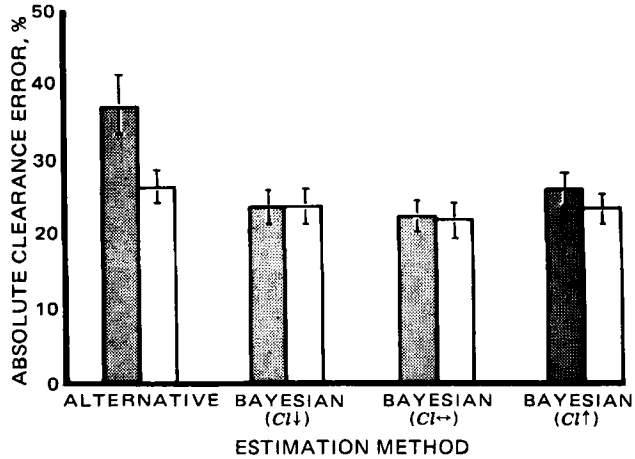

Figure 1—*The mean percent absolute error (true clearance minus predicted clearance expressed as a percent of the population mean clearance) for predictions by the alternative methods and the Bayesian method are shown. Dark bars refer to example 1. Clear bars refer to example 2. Lines at tops of bars show the 95% confidence intervals for the mean percent absolute errors. Three performances for the Bayesian method are shown; the center one (Cl ↔) corresponds to adjusting clearance in correct proportion to differences between observed and predicted levels. The performance marked Cl↓ (Cl↑) refers to clearance predictions made when adjusting clearance less (more) than appropriate. The absolute error of the Bayesian method is significantly smaller ($p < 0.05$) than that of the alternative method for all but the clear bar, Cl↓ case.*

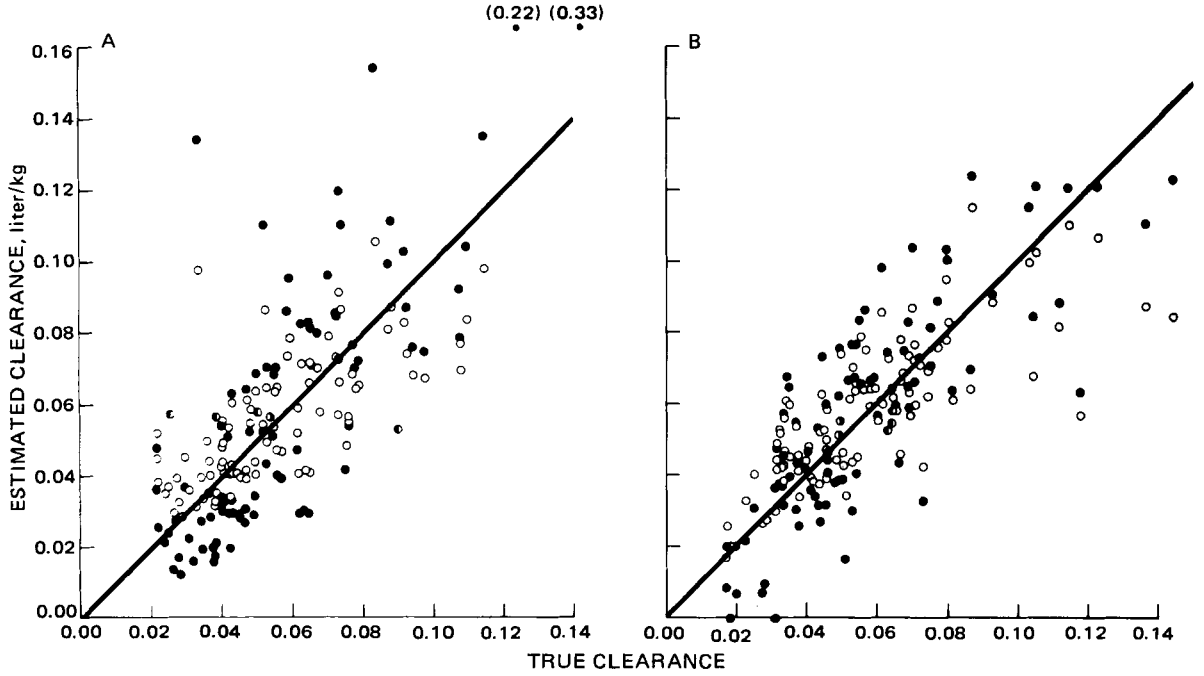

Figure 2—*Plots of predicted clearance* versus *true (simulated) clearance for predictions by the Bayesian (○) and alternative (●) methods. The diagonal line on each graph is the line of identity. A shows results for example 1; B shows results for example 2.*

The results for precision (absolute error) are different. The precision of the Bayesian method estimates typically exceeded that of the alternative method estimates. This was true whether or not the Bayesian method standard deviation ratios were correct or not, although some degradation of performance with incorrect ratios was seen. In the first example, the absolute errors of the alternative method were typically 50–70% larger than those of the Bayesian method, while in the second they were 10–25% larger.

Figure 1 illustrates the precision results of Table I. For the Bayesian method, the cases in which the ratio of ω_1 to σ was incorrect are not shown, as the performances in those cases were little different from those in which the correct ratios were used (Table I).

Figure 2 shows the predictions of the Bayesian and alternative methods for all 100 simulated points for both examples.

DISCUSSION

Various methods for revising estimates of individual pharmacokinetic parameters based on measured drug levels have been put forward. Most previously suggested methods for doing so can be criticized for not attempting to integrate already available information regarding population pharmacokinetic behavior with the information from the observed drug concentrations. A previous study (3) has pointed out that such behavior is not optimal, and has presented a general (Bayesian) framework that allows use of all available information at all times.

In this paper the Bayesian method is seen as an example of weighted least-squares estimation. This leads directly to a simple implementation of the method involving only minor modifications to any standard nonlinear weighted least-squares computer program (see *Appendix*).

In this paper the Bayesian approach has been applied to simulated data, representing two dosage adjustment examples for which other investigators have proposed alternative approaches. In both cases, the Bayesian method is superior to the alternative. Moreover, the former is relatively insensitive to major inaccuracies in some of the parameters it uses. This finding supports the suggestion (see *Appendix*) to use approximate values for those parameters when their true values are in doubt.

Regarding the simulations, one further point merits comment. The similarity of the magnitude of the errors for the Bayesian method in the first and second examples may, at first, seem surprising, since the first example uses only one measured level, while the second uses two. However, it should be recalled that the first level in the second example essentially substitutes for knowledge of initial dosage so that all the drug level information, *per se*, is actually confined to the second level.

Regarding the generality of the Bayesian approach, the basic method can be extended to arbitrary dosage and blood sampling patterns (9), numbers of samples, and pharmacokinetic models (10). In contrast, most other estimation methods, including the alternative ones evaluated herein, apply only to specific models or dosage patterns.

Regarding the theoretical advantages of the Bayesian approach, the most important one is its use of population information at all times. By using population information even when individual observations are available, the Bayesian method must perform better than methods that do not. Figure 2 illustrates this point. The clearance estimates from the Bayesian method seen there tend to err in the direction of the population mean (for true clearances less than the mean, Bayesian estimates tend to be high, and *vice versa*), while those of the alternative methods do not demonstrate this tendency. Rather, they can be quite erratic and have large associated errors. See the off-scale points in Fig. 2A. Even when absolute error is modest, the non-Bayesian estimates can be quite misleading. See the several instances in Fig. 2B where clearance is estimated by a previous method (1) to be at or near zero. The first example is an instance in which random error causes the observed levels to differ greatly from the corresponding true levels. The second occurs when the error, no matter what its magnitude, represents a large fraction of the true difference, which itself may be quite small. The non-Bayesian methods trust the observations implicitly, and will often magnify small differences from expectation in these so as to produce large estimation errors. In contrast, the Bayesian method discounts observations, the more so the more they are in conflict with (prior) parameter expectations. In some cases this conservatism will mean that a parameter truly different from expectation will be incorrectly regarded as closer to expected than it really is—at least until further drug levels are obtained. The incorrect discounting of truly unusual responses is more than compensated by the correct tendency to discount falsely unusual ones. Indeed, the Bayesian method is likely to perform well in precisely those circumstances in which other methods do not perform well: when observed drug levels actually provide little information about the parameters of interest.

APPENDIX

Implementation of the Bayesian method involves the use of suitable computer programs. The availability of a computer program that can perform parameter estimation using nonlinear weighted least squares is assumed[1]. Although large programs running on large machines are often

[1] A users manual and listings of computer programs that implement the above approach on a microcomputer are available. The authors should be contacted for information on obtaining these items.

used for this purpose [*e.g.*, NONLIN (11)], short programs that run on a microcomputer are also available (12).

Nonlinear weighted least-squares programs usually require at least the following: (*a*) data, consisting of a series of observations, $Z = (Z_1,Z_2,\ldots Z_N)$ and corresponding weights, $W = (W_1,W_2,\ldots W_N)$; (*b*) a subroutine that for each Z_i accepts as arguments a list of independent variable values (X_i) and a list of current parameter estimates (P), and produces as output, a prediction ($\hat{Z}_i$) of Z_i, as a function $[f(P,X_i)]$ of its arguments. Some programs are less sophisticated than others and restrict one to scalar X_i, usually denoting time, t_i. The following procedure for specifying (*a*) and (*b*) for a nonlinear weighted least-squares program is designed to function even with that restriction. These programs will also require other arguments, such as the maximum number of iterations allowed, the convergence criterion, *etc.* Specification of these is no different for the current application than it is for the usual ones.

It is assumed that there are N observations of drug levels, and s pharmacokinetic parameters to be estimated ($s + 1$ estimates are needed when an initial level is used). Further, it is assumed for now that the vector of mean population parameters, θ, is known as is ω_1 through ω_s and σ^2.

Any nonlinear weighted least-squares program can be used to find the P minimizing expression (5), by fulfilling requirements (*a*) and (*b*), as follows:

(*a*) The data: There are a total of $N + s$ observations. For $i = 1,\ldots,N$, let $Z_i = y_i$ and $W_i = 1/\sigma^2$. For $i = N + 1,\ldots,N + s$, let $Z_i = \theta_k$ and $W_i = 1/\omega_k^2$, where $k = i - n$.

(*b*) The subroutine: Let one component of X_i, X_{li}, say, be defined by $x_{li} = t_i$ if $i \leq n$ and $X_{li} = -(i - N)$ if $i > N$. Then the subroutine should return $\hat{Z}_i = f(P,X_i)$ if $X_{li} \geq 0$, but it should return $\hat{Z}_i = p_k$ where $k = -X_{li}$, if $X_{li} < 0$.

When the initial level idea is to be used, one does not regard the initial level as one of the N others. Rather, one modifies the data by adding observation number $N + s + 1$, corresponding to the new parameter, number $s + 1$. Then for $i = N + s + 1$, $Z_i = y_0$, $W_i = 1/\sigma^2$ and $X_{li} = -(s + 1)$, where y_0 is the measured value of the initial level. The subroutine need not be modified from its specification above.

The sole remaining problem is that of obtaining values for the population parameters, σ^2, θ, and ω_1 through ω_s. Methods for analyzing patient data in order to estimate population parameters have previously been presented [*e.g.*, (13)]. Many investigators have studied normal volunteers or selected patient populations and have published equations that predict average pharmacokinetic parameters as a function of body weight, renal function, and other factors. Recently, a compilation of such parameters for selected drugs has been assembled (14).

Available information, however, is often of varying quality and completeness. In particular, estimates of ω_1 through ω_s and σ^2 are least available, and, when available, least reliable. When this is the case, it is proposed not that the Bayesian method be abandoned, but that certain rules of thumb be used. For many pharmacokinetic parameters, a coefficient of variation, CV_1, of interindividual variability that is on the order of 25–50% is not uncommon, with volume of distribution often at the lower value and clearance at the upper (12). This variability is present after correcting for age, sex, renal function, and other observable patient features. A reasonable coefficient of variation, CV_2, of y, given P, is often 5–15%, since the ϵ error includes not only assay error but model misspecification error and error due to intraindividual kinetic variability. To compute an estimate of ω_k^2 and σ^2, the only further information needed are the values of θ_k and a typical value for y, a value in the therapeutic range; let the latter be denoted $\tilde{y}$. Then, for example, for $CV_2 = 10\%$, $\sigma^2 = (0.1\tilde{y})^2$, and for $CV_1 = 50\%$, $\omega_k^2 = (0.5\theta_k)^2$.

It is the author's experience that the Bayesian estimates are not too sensitive to the choices involved in this rule of thumb, while the ordinary least-squares estimates can be rather poor in comparison when sample size, N, is small. Of course when $N < s$, the ordinary least-squares estimates do not exist, whereas the Bayesian estimates do.

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