Computer-aided drug dosage*

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INTRODUCTION

Major efforts have been devoted to the application of computational techniques to medical diagnosis, a difficult computational task. The amount of information necessary to perform an exhaustive diagnostic search is formidable large. The "costs" associated with making certain diagnoses or eliminating others often affect a tentative diagnosis as much as the probabilities of the conditions being considered. These "costs" are usually intuitively considered by the physician and usually are not available as numerical quantities to use in a linear programming algorithm. Lastly, diagnosis is done both rapidly and well by most physicians.

In contrast stands therapeutics, specifically the administration of medicines. After deciding what and how much effect is desired (choosing the drug and the therapeutic objective) the problem is how much to give and in what temporal pattern. Drug-dosing is inherently quantitative and is presently done suboptimally. Accordingly, we have approached the construction of algorithmic techniques for determination of drug dosage.

Since drug effects correlate far better with drug levels in the body than with doses administered, a Target Blood Level (TBL) approach to drug administration seems reasonable. In order to implement such an approach, estimates of appropriate pharmacokinetic parameters for individual patients must be obtained so that pharmacokinetic models, providing the mathematical framework for drug level predictions, can be used to determine optimal dosage regimens. We have described a conceptual scheme and associated statistical methodology to accomplish this objective. In this paper, we summarize the scheme and methods, provide justification for our approach, report early results, and describe some future plans.

BACKGROUND

Eighteen to thirty percent of all hospitalized patients sustain one or more adverse drug reactions and the duration of their hospital stay is nearly doubled as a result. In addition, 3 to 5 percent of all admissions to hospitals are primarily for a drug reaction and 30 percent of these patients have another drug reaction during their hospital stay. The economic consequences of these reactions are staggering: one-seventh of all hospital days is devoted to the care of drug toxicity, at an estimated annual cost of 3 billion dollars. The same amount would cover the cost of all prescription drugs used in this country per year.

An encouraging aspect of the large adverse reaction rate is that 70-80 percent of them are direct extensions of the pharmacologic actions of the drugs involved, and therefore should be predictable and preventable. The majority of the pharmacologic adverse reactions are probably not the result of extraordinary individual sensitivity to the actions of the agent, but rather of dosage regimens leading to inordinately high blood levels.

The evidence which associates drug levels in blood or tissues with their effects is striking. It is particularly clear-cut for those drugs responsible for more
than 50 percent of dose-related adverse reactions, digitalis preparations, anti-arrhythmic drugs, and antimicrobials. As an example, consider digoxin, a drug which, in clinical practice, is both highly useful and formidably toxic. About 20 percent of all patients receiving the drug demonstrate pharmacologic toxicity and as many as 30 percent of those demonstrating such toxicity may die of it. A three-or-more-fold variation in the blood levels of digoxin is seen in different individuals given the same doses of the agent, but toxicity is highly correlated with blood levels: in one study, 90 percent of individuals with levels less than 2 nanograms/ml of plasma were nontoxic and 87 percent of those with levels greater than this amount were toxic. For digoxin, then, individual sensitivity differences may account for as little as 10 percent of clinical toxicity.

That levels of drugs in body fluids should bear a more constant relationship to effects than doses administered is readily understandable. Drugs act on receptors and elicit effects which are proportional to the fraction of occupied receptors. The concentration of a drug at its receptor is a major determinant of drug effect. The utility of blood levels stems from the observation that although few drugs act on receptors in the blood itself, after drug distribution, tissue concentrations of drugs (presumably at their sites of action) bear a reasonably linear and constant relationship to blood levels. Individual variation in absorption, distribution, metabolism and elimination of drugs, however, causes widely varying blood levels to be found in different individuals, despite standard doses.

It seems clear, then, that a TBL approach to drug dosage design is theoretically sound and likely to be beneficial. Pharmacokinetic models can represent and quantify variations in absorption, distribution, metabolism and elimination of drugs. In order to utilize a pharmacokinetic model for the purpose of drug dosage design, some way of predicting individual variation in the parameters of the model must be available. An obvious approach is to measure blood levels of agents at varying time intervals after administration of a standard regimen and to adjust the parameters of the model to yield a best fit to the observed levels. This is analogous to the way in which most physicians administer drugs today: a standard regimen is begun, effects are observed (presumably proportional to levels) and dosage adjustments are made based upon these observations. The quantitative adjustments are more intuitive than optimal. We can do better than merely improve the quantitative aspects of the feedback process described above, although doing only this can lead to excellent results.

The factors responsible for pharmacokinetic variation can be related to the physiological determinants of pharmacokinetic processes. For example, digoxin is primarily eliminated by renal excretion. The elimination rate of the drug should be, and is, proportional to renal function. Tests designed to assess renal function [such as measuring the serum creatinine or Blood Urea Nitrogen (BUN)] are routine. These measurements can be used to modify the dosage regimen of digoxin in accord with the excretory ability of the individual patient.

The combination of prior clinical information with quantitative feedback adjustment should produce a system for optimal drug dosage design. In order to do this we require a black box with the following characteristics: the inputs are clinical data, commonly and easily available (such as height, weight, age, sex, and the results of standard laboratory tests, e.g., tests of renal function); the outputs are a set of predicted values for the parameters of a pharmacokinetic model. On the basis of these predicted parameter values, the initial dosage of a drug can be set to produce the TBL. As additional data in the form of blood level measurements or changes in the laboratory tests become available, estimates of the parameters can be optimally modified (by the black box) to improve dosage suggestions.

THE DOSE—BLOOD LEVEL RESPONSE MODEL

The first task in the design of the black box is to formulate a model for the relationship between the

<table>
<thead>
<tr>
<th>Table I—The Conceptual Scheme</th>
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<tbody>
<tr>
<td>I. Observations (O) → Physiologic Variables (P)</td>
</tr>
<tr>
<td>type: usually non-linear</td>
</tr>
<tr>
<td>data source: general population</td>
</tr>
<tr>
<td>example: Body Surface Area (BSA) = F (height, weight)</td>
</tr>
<tr>
<td>II. P → Pharmacokinetic Variables (Q)</td>
</tr>
<tr>
<td>type: linear</td>
</tr>
<tr>
<td>data source: patients receiving drug</td>
</tr>
<tr>
<td>example: Volume of Distribution (Vd) = F (BSA)</td>
</tr>
<tr>
<td>III. Q → Pharmacokinetic Parameters (K)</td>
</tr>
<tr>
<td>type: usually non-linear</td>
</tr>
<tr>
<td>data source: theoretical</td>
</tr>
<tr>
<td>example: Rate Constant of Elimination (Kel) = Clearance/Vd</td>
</tr>
<tr>
<td>IV. K → Blood Level Predictions</td>
</tr>
<tr>
<td>type: non-linear pharmacokinetic model</td>
</tr>
<tr>
<td>data source: theoretical</td>
</tr>
<tr>
<td>example: one compartment model with first order absorption</td>
</tr>
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</table>
clinical data and the pharmacokinetic parameters. Our model is outlined in Table I. Clinical observations (O) are used to predict physiological variables (P). These predictions can be defined through study of the general population and need not be restricted to those individuals who have received the drug of interest. The relationships are not restricted as to type; they may be linear, non-linear, discontinuous, etc. The example given in Table I, Body Surface Area (BSA), is a quantity estimated from a non-linear function of height and weight and is expected to be more linearly related to metabolic capacity and body "compartment" sizes than either height or weight. In Table I, the pharmacokinetic model itself is a simple one: the one-compartment open model with first order absorption. Its parameters (K) are: Kel, the first-order rate constant of elimination of the drug; Vd, the volume of distribution of the drug; and a series of Ka's and f's, each pair representing the rate constant of absorption and the fraction of dose absorbed for a specified route of administration. The K may be linearly related to the P. For example, the Vd of a drug might be predictable from a patient's body surface area, as shown in Table I. A non-linear function of a K might bear a linear relationship to one or more of the P. An example is the clearance of a drug (the product of Kel and Vd) which would be linearly related to a P describing renal function (the Glomerular Filtration Rate, GFR) if the drug were eliminated by the kidneys. To keep the scheme general, a set of pharmacokinetic variables, Q (distinct from the K) are defined as functions, again of any variety, of the K. The Q are defined wholly from theoretical considerations. Finally, having defined the P and Q so that we expect linear relationships to hold between them, we assert that they are related linearly. The first data-fitting task is that of estimating the coefficients of the linear P to Q transformation. This can be done utilizing data from individuals whose clinical observations are known and whose blood levels of drug have been measured.

The full model allows utilization of general population data and prior information in the form of both theoretical relationships and constraints on the coefficients to be estimated for the P to Q transformations. The use of an extremely simple pharmacokinetic model is justified on two grounds. First, for clinical medicine, our scheme must be responsive to shifts in patient characteristics and inexpensive to operate. More parameters imply more data-fitting, degrading responsiveness, and increasing cost. Second, most drugs with clinical utility do not cause significant toxicity until their blood levels are at least twice those at which significant efficacy is achieved. Therefore, there is no need for great precision; prediction errors of 50 percent should have little clinical import.

Before discussion of the problem of merging feedback (blood-level) information with initial estimates, some preliminary tests of the appropriateness of the conceptual scheme and of the ability to estimate coefficients for the P to Q relationship will be presented.

TEST OF THE MODEL

Dr. Thomas Smith of the Massachusetts General Hospital kindly supplied us with clinical data, dosage history, measured blood levels (one per patient) and determinations of the presence or absence of toxicity in a group of 90 patients who received digoxin. The clinical data for each patient consisted of age, weight and BUN. Fifteen patients were questionably toxic and 18 definitely toxic by published criteria. The model was adapted to digoxin from the available clinical data, by using weight as a predictor of BSA, and age, weight and BUN as predictors of renal function. Vd was assumed proportional to BSA. Digoxin clearance was assumed proportional to GFR and BSA since the non-renal losses of digoxin are presumably metabolic and should therefore be related to BSA. All digoxin had been administered orally so that Ka and f values for the oral route only were needed. Digoxin has an absorption value (f) of .85. While the precise rate of oral absorption is not known, it is sufficiently rapid relative to rates of elimination that an arbitrary large value could be assigned to the oral-rate constant of absorption without expected loss in accuracy. Data was adequate to establish an expected value for Kel for normal individuals, and to support the assumption that digoxin clearance should be linearly related to GFR. Data on the rate of non-renal loss of the drug is scanty, and no clear data exist for estimating the relationship between BSA and Vd. Accordingly, the patient data were first used to estimate these values using standard non-linear data fitting techniques. The blood levels were weighted by the inverse of the observed values plus the measurement error in their determination because, on the one hand, with unweighted measurements, fitting to absolute errors inappropriately magnifies the importance of those patients with large measured blood level values, and, on the other hand, data fitting by pure relative error (corresponding to weighting by the inverse of the square of the measured value plus the measurement error variance) remove all bias toward greater predictive accuracy for higher values, which are the more clinically important ones, being indicative of toxicity.
We arrived at a value of 9 percent per day non-renal loss (as opposed to an estimate of 14.4 percent per day\(^{10}\)) and a Vd value of 351 liters/square meter of BSA. It is noteworthy that these estimates could be easily obtained from the crude clinical data at our disposal. The use of our scheme permits estimation of population values for pharmacokinetic quantities from usual clinical data and does not demand separate and elaborate experiments. This point is crucial, since an individual blood level determination obtained from clinical usage of the feedback portion of the system will not only serve to improve the estimates of that individual's responses, but also add to the data base, making improved population estimates possible.

With the scheme set for digoxin and necessary values obtained from the literature, or as noted above, from the data itself, the ability of the scheme to predict blood levels of the patients, using various amounts of prior clinical information, was examined. Table II shows the resultant correlations. The only upward bias in utilizing the correlation coefficients to describe the predictive capacity of the system stems from the use of one degree of freedom for the estimation of the non-renal losses, since Vd operates in the pharmacokinetic model as a scale factor only. The fraction of total variance in the actual levels which is explained by the computed levels is expressed by \(r^2\); in the absence of any clinical data save the dose administered, only 8 percent of the level variance is explained, while use of all the clinical data allows explanation of 54 percent of the variance. Knowledge of renal function makes the major contribution to accurate predictions, but the patient's weight, the sole predictor of size used, explains as much of the variation in levels as does the dose. In order to exclude the possibility that the few very high values present in the data were responsible for the high correlation we obtained, despite our weighting scheme, predictions were examined when weighted by the inverse of the square of the measured value plus the measurement error variance. Under these conditions, the correlation coefficient for predictions made with full information fell only to .71.

More important, however, than the ability to predict the measured values with a modest degree of accuracy, is the potential clinical implication of the predictions. As has been mentioned, digoxin levels greater than 2 ng/ml are associated with a significant incidence of toxicity. Table III compares the toxicity predictions of the actual measured levels, using this cut-off point, with those of the predicted levels. Although the predicted values are not quite as good at predicting toxicity as are the measured values (there are, however, no significant differences in the columns of Table III by \(x^2\) analysis), use of the scheme might have prevented 10 of the 18 toxicities in this group of patients. Clearly the potentially prospective availability of the predictions and the non-toxic dosage schemes they would engender outweigh the slight (retrospective) diagnostic advantage of the actually measured levels.

**THE FEEDBACK PROCESS**

The requirement for feedback adjustment of the model parameters is that it make an orderly transition from estimates of an individual's pharmacokinetic parameters based solely upon population data to ones based to a greater extent upon measured blood levels of the drug. Our approach is based upon an estimation scheme valid in circumstances where an individual parameter vector characterizing responses (in our case, the Q vector "characterizes" the blood level "response") is dispersed about a population mean (that is, individual vectors are similar, but not identical).\(^{17}\) This regression method allows efficient estimation of the mean value of the parameter vectors in the population, of the extent of dispersion of individual parameters about the population mean, and of the

**TABLE II—Relation Between Program-Predicted and Actual Blood Levels of Digoxin in a Sample of 99 Patients**

<table>
<thead>
<tr>
<th>Information Used</th>
<th>Correlation Coefficient ((r))</th>
<th>(r^2)</th>
<th>(\sigma r^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Daily dose</td>
<td>.29</td>
<td>.08</td>
<td>–</td>
</tr>
<tr>
<td>2. 1 + model</td>
<td>.31</td>
<td>.10</td>
<td>+.02</td>
</tr>
<tr>
<td>3. 2 + weight</td>
<td>.42</td>
<td>.18</td>
<td>+.08</td>
</tr>
<tr>
<td>4. 3 + age</td>
<td>.47</td>
<td>.23</td>
<td>+.05</td>
</tr>
<tr>
<td>5. 4 + BUN</td>
<td>.73</td>
<td>.54</td>
<td>+.31</td>
</tr>
</tbody>
</table>

**TABLE III—Comparison of Predictions of Digoxin Toxicity by Actual and Program-Predicted Blood Levels**

<table>
<thead>
<tr>
<th>Levels Used</th>
<th>Predictions of Toxicity</th>
<th>False +</th>
<th>False -</th>
<th>Total Correct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual</td>
<td></td>
<td>10/66</td>
<td>3/18</td>
<td>71/84</td>
</tr>
<tr>
<td>Program-predicted</td>
<td></td>
<td>11/66</td>
<td>8/18</td>
<td>65/84</td>
</tr>
</tbody>
</table>
values of the parameter vectors characterizing each individual. In our case, population data is used to estimate a mean population Q vector, the appropriate adjustments to be made in this vector for the values of clinical observations, a population variance matrix of parameter prediction error, \( \Lambda \), and the variance of prediction error associated with individual blood levels, \( \sigma^2 \). An individual’s Q vector is assumed to be the sum of the population mean vector adjusted for his set of clinical observations, plus an individual shift vector, originally unknown, with mean value, zero. For initial dosage suggestions, the shift vector is assumed to be zero. For the feedback portion of the system, given \( \Lambda \) and \( \sigma^2 \) and the actual versus predicted blood level for the individual, a non-zero value is assigned to the individual shift vector so as to maximize the prediction likelihood function (an empirical Bayes estimator). A more complete description of the statistical methods underlying this approach can be found in References 1 and 18. What occurs, in effect, is that the information content of a blood level measurement is used to decrease the uncertainty of our knowledge of the components of an individual’s Q vector (and hence his K vector) so as to minimize the mean square error in the resulting blood level predictions.

**TEST OF THE ESTIMATION SCHEME**

Examination of the problems attendant upon estimation of a population dispersion matrix has begun. The simpler case of an underlying response model linear in the explanatory variables (the P) was studied first. Despite the linearity of the underlying model, an analytic solution is not apparent for the dispersion matrix; thus, even in the linear case, one is forced to use non-linear techniques to maximize the likelihood function. For this reason the linear and non-linear cases share many characteristics. If efficient estimation of a dispersion matrix could not be accomplished in the linear case, we would be pessimistic about the ability to do so in the non-linear case. The problem can be reduced to a search over the space of triangular matrices, \( T \), such that \( TT' = \Lambda \). The number of parameters to be estimated by non-linear methods is therefore \( p = k(k+1)/2 \), where \( k \) is the dimension of \( \Lambda \). The Fletcher-Powell algorithm has been used to seek a maximum of the likelihood function over this space. The results of simulations to date have been uniformly encouraging. The likelihood function is smooth and well behaved, and is well described by analytical derivatives. Regardless of the initial estimate chosen for \( T \), the search algorithm converges to the same maximum and the same estimate for \( \Omega \), indicating that the likelihood function has a unique extremum. Convergence appears to require fewer than 3p iterations in all but a few cases, and 4p iterations has been the maximum. Thus the non-linearity of the problem appears to pose no difficulties.

More important, a relatively small amount of data appears sufficient to generate a satisfactory estimate of \( \Lambda \). With four simulated observations on each of forty individuals, the estimates have consistently approximated the relative magnitudes of the diagonal elements of \( \Lambda \), and the signs and magnitudes of the off-diagonal elements.

**CURRENT WORK**

The preliminary results obtained in the development of both the conceptual and estimation schemes has been encouraging. For the initial prediction portion, it was a simple matter to write an interactive program to run in a time-shared mode (for use via a remote access terminal) which would accept clinical observations on a patient as well as the (physician determined) TBL and deliver a dosage scheme (at present, for digoxin only) adjusted for the individual, and designed to produce the TBL. We note that although it is possible to provide information on the usual range of therapeutic blood levels for a drug through the program, the actual TBL for an individual patient should not be pre-programmed. It is precisely in the choice of this value that the physician is called upon to exercise his judgment as to the severity of the condition being treated, the therapeutic objectives sought and the projected sensitivity of his patient.

The interactive program and the initial dosage suggestions are being tested in a prospective fashion. Out-patients in need of digitalis or in need of adjustment of digitalis therapy are being studied. Both the primary physician and the program are suggesting regimens and predicting blood levels for these patients. The program output is made available to the physician for a randomly selected portion of the patients, and the physicians administer the drug as they see fit. Comparisons will be made in the accuracy of blood level predictions by the physicians and the program, and in the results of treatment (both for efficacy and toxicity) obtained by administration of program-suggested regimens.

The estimation scheme is being further tested by Monte Carlo studies. Multiple blood level data is being
obtained on patients receiving digoxin so that the procedures for estimation of $A$ can be tested. The questions of major interest are: (1) How much data is necessary to estimate $A$ and how valuable is knowledge of the population dispersion in predicting individual blood levels? (2) What is the “trade-off” between clinical observations and subsequent blood level determinations; e.g., how many blood level determinations does it take to make up for lack of knowledge of renal function? (3) Do blood levels drawn early in the course of therapy, when maximum blood levels are not yet attained and toxicity is highly improbable, contribute substantially to the ability to predict future (maximum) blood levels? (4) At what point is the further determination of blood levels unnecessary; that is, when do they cease to contribute new information? We expect to have partial answers to these questions for digoxin at the time of the Spring Joint Computer Conference, and will devote the major portion of our presentation to discussing them.

SUMMARY AND CONCLUSION

We have devised a conceptual scheme which successively relates routinely available clinical observations to measures of underlying physiologic and pharmacokinetic factors and, ultimately, to pharmacokinetic parameters. These parameters can be used in a pharmacokinetic model to produce optimal initial dosage suggestions tailored to individual needs. We have also proposed a statistical methodology for adjustment and improvement of individual estimates in the light of subsequent response data. Preliminary tests of the various portions of the system have been uniformly encouraging. The scheme is highly general; most of the definable influences on drug absorption, distribution, metabolism and elimination can be represented, quantified, merged with others and tested in relation to blood level data. As a consequence of the statistical techniques used and the degree to which extensive exploitation of prior information is possible, determination of even a single blood level for an individual should markedly improve the system's predictive accuracy for him. Drug levels determined in order to improve treatment for an individual also contribute to the underlying data base used to update the various estimated population coefficients. Thus, the system can learn. A broad definition of what constitutes clinical observation will allow us to use the pharmacokinetic variables determined for one drug, for one patient, in the estimation of the pharmacokinetic parameters for another drug for him, if a meaningful relationship holds between them. Hence, the system is a research tool.

REFERENCES

1 L B SHEINER B ROSENBERG K L MELMON
Pharmacokinetic modelling for individual patients: A practical basis for computer-aided therapy
Comp and Biomed Res submitted 1971
2 L G SEIDL T G THORNTON J W SMITH et al
3 B C HODDINOTT C W GOWDEY
W K COULTER et al
Drug reactions and errors in administration on a medical ward Can Med Assoc J 37: pp 1001-1006 1967
4 N HURWITZ
Admissions to hospital due to drugs Br Med J 1: pp 539-549 1969
5 K L MELMON
6 R I OGILVIE J RUEDY
Adverse drug reactions during hospitalization Can Med Assoc J 37: pp 1450-1457 1967
7 T W SMITH V P BUTLER E HABER
8 J T BIGGER D H SCHMIDT H KUTT
Relationship between the plasma level of diphenylhydantoin sodium and its cardiac antiarrhythmic effects Circ 38: pp 363-374 1968
9 J KOCH-WESER S W KLEIN
Procainamide dosage schedules, plasma concentrations, and clinical effects JAMA 216: pp 1454-1460 1971
10 C M KUNIN
11 G A BELLER T W SMITH
W H ABELMANN et al
12 T W SMITH E HABER
13 L B SHEINER
14 J E DOHERTY W H PERKINS
M C WILSON et al
15 J E DOHERTY  
_The clinical pharmacology of digitalis glycosides: A review_  

16 R W JELLIFFE  
_A mathematical analysis of digitalis kinetics in patients with normal and reduced renal function_  
Math Biosciences 1: pp 305-325 1967  

17 C R RAO  
_The theory of least squares when the parameters are stochastic_  
Biometrika 52: pp 447-458 1965  

18 B ROSENBERG  
_Linear regression with stochastically dispersed parameters_  
Biometrika submitted 1971