Use of Limited Laboratory-Acquired Therapeutic Drug Monitoring Data in Determining Individualized Drug Requirements*

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ABSTRACT

 Routinely acquired therapeutic drug monitoring (TDM) data from 220 patients were used to estimate patient-specific pharmacokinetic parameters for the following drugs: aminoglycoside antibiotics (gentamicin and tobramycin), digoxin, theophylline, carbamazepine, procainamide, phenobarbital, and quinidine. A microcomputer based set of algorithms operating on two relatively unconstrained TDM values estimated pharmacokinetic parameters with which future TDM levels were forecast. Mean prediction errors (mpe) and root mean squared errors (rmse) were used as measures of predictive performance. Values of mpe deviated from zero by less than one |Jg per l for digoxin and by less than one mg per l for all other drugs. Values of rmse were also small when viewed in the context of the respective therapeutic plasma concentration ranges.

Introduction

The simultaneous evolutions of analytical technology and applied pharmacokinetics are beginning to change the scope and purpose of therapeutic drug monitoring (TDM). Analytical developments now permit rapid turn-around times for reporting TDM values. Recent advances in applied pharmacokinetics permit the estimation of pharmacokinetic parameters from limited TDM data. For example, estimates of pharmacokinetic parameters from as few as two plasma concentration measurements have been described by Chiou et al for theophylline5 and by Zaske et al for aminoglyco-

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side antibiotics. Ball has described a computer-based algorithm for estimating kinetic parameters from two concentration measurements for drugs with linear, one-compartment kinetics. A computer program for estimating pharmacokinetic parameters from one or more concentration measurements has been published by Sheiner, which executes calculations of individualized pharmacokinetic parameters from limited TDM data by both ordinary least squares (OLS) and modified Bayes procedures.

A limited experience with a computer-based strategy for estimating pharmacokinetic constants from limited TDM data has been recently described. Initial experience was limited to aminoglycoside (AG) antibodies, and theophylline. Our objective was to evaluate the predictive performance of a computer-based strategy which estimates pharmacokinetic constants from limited TDM data by gauging the accuracy with which those estimated constants could predict future TDM values. The drugs of interest were AG antibiotics, theophylline, digoxin, carbamazepine, procainamide, phenobarbital, and quinidine.

Method

Patient Selection

Patients were approached for written, informed consent after approval to do so had been secured from attending physicians. Written consent was obtained from parents or guardians of minors. Participating patients, in fact, basically consented to allow access to laboratory and chart information. Patients were identified as candidates for the study on the basis of TDM analyses. All analyses were performed in accordance with routine procedures of the toxicology laboratory. Only those individuals with at least two TDM measurements for one of the following drugs were candidates: gentamicin, tobramycin, theophylline, digoxin, carbamazepine, phenobarbital, procainamide, and quinidine. Only those patients for whom at least three TDM levels had been measured were ultimately included. Thus, participation required no additional phlebotomy beyond that which was required for routine TDM.

No instructions were issued to either the medical or nursing staffs with regard to sampling times. The following types of TDM data were excluded from consideration: (1) levels drawn during the infusion of intermittent intravenous infusions, (2) levels drawn during the absorptive phase (oral formulations), and (3) levels surrounding a drug dose when the timing of the dose could not be estimated.

Analyses

All assays were performed by the toxicology laboratory of the Medical College Hospital in accordance with the laboratory's routine TDM protocols. Each sample was assayed in singlet. The laboratory is a participant in three quality control programs and is approved by the College of American Pathologists. All assays were performed by fluorescence polarization immunoassay using a TDx analyzer.* Day-to-day coefficients of variation for a three week interval were as follows: gentamicin, 5.3 percent; tobramycin, 3.9 percent; theophylline, 3.5 percent; digoxin, 14.4 percent; carbamazepine, 7.5 percent; phenobarbital, 3.9 percent; procainamide, 5.5 percent; and quinidine, 4.2 percent.

Estimation of Pharmacokinetic Parameters

Pharmacokinetic parameters for individual patients were estimated from two TDM measurements using a computer-based series of algorithms designated as Pharmatrol. Input information included: (1) patient weight, (2) dosing
history including amounts, formulation(s), times of administration, route(s) of administration, (3) times at which blood samples for TDM were drawn, and (4) two TDM values. The version of Pharmatrol employed operates on an IBM PC AT microcomputer and is written in BASIC. The solution for individualized kinetic parameters executed by Pharmatrol is broadly similar to other existing computer-based strategies which invoke least squares minimizing algorithms with or without Bayesian weighting terms.

**Measurement of Predictive Performance**

As prior pharmacokinetic data on individual patients were non-existent, the following approach to assessing Pharmatrol’s predictive performance was used. From the first two TDM levels on participating patients, individualized kinetic parameters were calculated. Subsequently, those parameters together with charted doses were used to calculate (predict) drug plasma concentrations at the time at which the third TDM level was drawn. The difference between predicted and measured third TDM levels was taken as the prediction error. The mean prediction error (mpe) was considered a measure of prediction bias, and the 95 percent confidence limit of the mpe and the root mean squared error (rmse) were viewed as measures of prediction precision as described by Sheiner et al. Differences between mean observed and predicted third TDM levels were also compared with a paired *t* test (two-tailed), and considered significant at *p* < 0.05.

**Results**

Two hundred thirty-two (232) analyses were performed on 220 patients. Of these, 120 were males. General patient characteristics are described in table I. The overall range was from three months to 93 years. The overall weight range was from 2.3 to 171.8 kg. Patients were also extremely diverse in measures of renal and liver function. In table I are provided means, SD, and ranges for ages, weights, and laboratory values in our patient material. Also shown are the number of male (M) and female (F) patients. For the AG antibiotics, gentamicin, and tobramycin, 66 percent of the first TDM levels were troughs, 10 percent were peaks, and 25 percent were mid-dose levels where mid-dose refers to a post-infusion sample that is neither a peak nor a trough. Forty percent of the second TDM levels were troughs, 46 percent peaks, and 14 percent mid-dose levels. Thirty-two percent of the third levels were peaks, 54 percent troughs, and 14 percent mid-dose levels. For theophylline, three formulations tended to

<table>
<thead>
<tr>
<th>TABLE I</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Characteristics</strong></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (year)</th>
<th>Weight (kg)</th>
<th>SCR (mg/dl)</th>
<th>Albumin (g/dl)</th>
<th>SGOT (units/l)</th>
<th>SGPT (units/l)</th>
<th>ALK P'TASE (units/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>51.6</td>
<td>64.7</td>
<td>1.3</td>
<td>3.4</td>
<td>45.2</td>
<td>30.3</td>
</tr>
<tr>
<td>SD</td>
<td>22.3</td>
<td>26.4</td>
<td>0.8</td>
<td>0.7</td>
<td>42.4</td>
<td>19.0</td>
</tr>
<tr>
<td>Range</td>
<td>0.25-93</td>
<td>2.3-171.8</td>
<td>0.2-6</td>
<td>1.5-5.2</td>
<td>6-458</td>
<td>6-154</td>
</tr>
</tbody>
</table>

Male = 120

Female = 100

$^{**}$SCR = serum creatine

$^{**}$SGOT = serum glutamic oxaloacetic transaminase

$^{**}$SGPT = serum glutamic pyruvic transaminase

$^{**}$ALK P'TASE = alkaline phosphatase
be used most frequently: aminophylline both orally and by intravenous infusion, and a sustained-release theophylline formulation. Several patients were switched from one formulation to another and one route of administration to another during the period in which three TDM levels were obtained. Most TDM levels represented mid-dose sampling times.

Digoxin was administered either intravenously or orally as a tableted formulation or elixir. The initial two TDM levels were collected as either mid-dose samples or troughs. The third levels were mostly troughs (90 percent) with the remaining levels representing mid-dose samples.

Carbamazepine was administered orally. Approximately 60 percent of all levels were troughs, and the balance were mid-dose levels.

Procainamide was administered either intravenously or as rapid release or sustained release oral formulations. Two patients were switched from the rapid release to the slow release formulation during the period in which TDM levels were obtained. Four patients were switched between the intravenous and oral sustained release formulations. Again, most levels represented mid-dose levels.

Phenobarbital was administered intravenously or orally using either tablets or the elixir. Three patients received both intravenous and oral formulations during the course of the analyses. The first two levels consisted of trough (50 percent) and mid-dose measurements. However, 80 percent of the third levels represented mid-dose values.

Both quinidine gluconate and sulfate were used orally. Five of the six initial levels represented troughs; one a mid-dose. Two of the second levels represented troughs; four were mid-dose levels. All of the third levels represented mid-dose levels.

The predictive performance of Pharmatrol is shown in table II. The mean prediction error and its 95 percent confidence limits and the root mean squared error are reported in units of plasma drug concentration since they represent the difference between predicted and actual third TDM levels. They have also been referenced for each drug to the therapeutic range by expressing them as percentages of the mid-range value. In table III are provided mean values for clearance (CL) for each drug. Data for gentamicin and tobramycin have been pooled under the heading of aminoglycosides since their pharmacokinetic parameters are very similar. Also shown in table III are the mean (± S.D.) values for observed and predicted third TDM levels. Only the differences between means for carbamazepine and digoxin were statistically significant.

Discussion

Newly developed computer-based strategies for estimating individualized pharmacokinetic parameters have recently evolved. One computer-based method, Pharmatrol, has been evaluated by us for its ability to predict future drug concentrations using patient-specific pharmacokinetic parameters calculated from two extant TDM measurements. This was done for seven drugs: AGs, digoxin, theophylline, carbamazepine, phenobarbital, procainamide, and quinidine. Mean prediction errors showed very little bias, and typically deviated by a fraction of one concentration unit from zero. Bias in prediction of the third TDM level was also low even when expressed as a percentage of the mid-range value of each drug's therapeutic range with predictions for carbamazepine and quinidine exhibiting only -10 percent and 15 percent bias, respectively, and predictions for all others exhibiting less than five percent bias.
TABLE II
Bias (MPE) and Precision (RMSE) of Third TDM Levels

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic Range*</th>
<th>N†</th>
<th>MPE‡</th>
<th>Percent</th>
<th>RMSE‡</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>&lt; 2.0 - 10.0</td>
<td>87</td>
<td>0.1</td>
<td>1.7</td>
<td>1.0</td>
<td>16.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(-0.04, 0.40)</td>
<td>(-0.7, 6.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td>8.0 - 20.0</td>
<td>49</td>
<td>-0.2</td>
<td>-1.4</td>
<td>2.2</td>
<td>15.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(-0.8, 0.5)</td>
<td>(-5.7, 3.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>0.7 - 4.0</td>
<td>48</td>
<td>0.1</td>
<td>4.2</td>
<td>0.4</td>
<td>17.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0, 0.2)</td>
<td>(0, 8.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>4.0 - 8.0</td>
<td>16</td>
<td>-0.6</td>
<td>-10.0</td>
<td>1.5</td>
<td>25.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(-1.4, 0.1)</td>
<td>(-23.3, 51.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>15.0 - 40.0</td>
<td>15</td>
<td>0.4</td>
<td>1.2</td>
<td>4.7</td>
<td>14.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(-2.3, 3.1)</td>
<td>(-7.1, 9.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procainamide</td>
<td>4.0 - 8.0</td>
<td>11</td>
<td>-0.1</td>
<td>-1.7</td>
<td>0.9</td>
<td>15.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(-0.8, 0.5)</td>
<td>(-13.3, 8.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinidine</td>
<td>3.0 - 5.0</td>
<td>6</td>
<td>0.6</td>
<td>15.0</td>
<td>0.9</td>
<td>22.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(-0.3, 1.4)</td>
<td>(-7.5, 35.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Therapeutic ranges represent reference ranges in use at the Toxicology Laboratory of the Medical College Hospital, Medical College of Ohio. Values are in mg/l except for digoxin (µg/l). Upper limit of the digoxin range is for neonates. Limits of 3 µg/l and 2 µg/l are used for children greater than one year and adults, respectively.

†N = number of observations

‡Values of MPE and RMSE are given in units of mg/l (except for digoxin, µg/l) and as a percentage of the mean of the therapeutic range for each drug (percent).

TDM = therapeutic drug monitoring.

Precision of third TDM predictions was also good, approaching 15 percent when referenced to mid-range values for all drugs except quinidine and carbamazepine for which rmse values were 22.5 percent and 25 percent, respectively.

Both the mpe and the rmse values were satisfactory for clinical purposes when viewed in the context of the normal therapeutic ranges of the drugs, though no reference range for such measures of predictive performance is available for

TABLE III
Mean Pharmacokinetic Parameters* and Predicted Third TDM Levels

<table>
<thead>
<tr>
<th>Drug</th>
<th>N†</th>
<th>Clearance (l·hr⁻¹·kg⁻¹)</th>
<th>Observed‡</th>
<th>Predicted‡</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>87</td>
<td>0.058 ±0.036</td>
<td>3.1</td>
<td>3.0 ±0.036</td>
<td>0.51</td>
</tr>
<tr>
<td>Theophylline</td>
<td>49</td>
<td>0.043 ±0.019</td>
<td>12.3 ±12.0</td>
<td>12.3 ±12.3</td>
<td>0.62</td>
</tr>
<tr>
<td>Digoxin</td>
<td>48</td>
<td>0.112 ±0.080</td>
<td>1.2</td>
<td>1.0 ±0.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>16</td>
<td>0.061 ±0.022</td>
<td>7.4</td>
<td>7.8 ±3.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>15</td>
<td>0.005 ±0.003</td>
<td>20.7 ±20.5</td>
<td>20.5 ±20.5</td>
<td>0.65</td>
</tr>
<tr>
<td>Procainamide</td>
<td>11</td>
<td>0.277 ±0.133</td>
<td>4.9</td>
<td>5.1 ±4.9</td>
<td>0.47</td>
</tr>
<tr>
<td>Quinidine</td>
<td>6</td>
<td>0.197 ±0.269</td>
<td>3.3</td>
<td>3.2 ±3.2</td>
<td>0.22</td>
</tr>
</tbody>
</table>

*Parameters are given as mean ± SD
†N = number of observations
‡TDM values for digoxin are in units of µg/l
§Significantly different from observed value by paired t test

TDM = therapeutic drug monitoring
comparative purposes. The means of predicted third TDM levels closely approximated the means of observed third TDM levels, and the differences between all means must be viewed as small in a clinical context even though the differences between mean observed and predicted third TDM levels for both digoxin and carbamazepine were statistically significant. However, for digoxin the mean of predicted third levels deviated by 8 percent from the mean of observed values. The extent to which the well-known phenomenon of digoxin assay interference by digoxin-like immunoreactive factors (DLIF) may have contributed is unknown, but must not be overlooked. These DLIF are known to elevate "apparent" digoxin levels by at least 0.2 µg per l.6 Approximately one-third of our subjects who were monitored for digoxin evidenced some renal impairment—a condition known to be attended by the appearance of DLIF.

For carbamazepine, the difference between the mean of observed and mean of predicted third TDM levels was 1.4 mg per l or 19 percent. Carbamazepine is known to be capable of inducing its own metabolism. Autoinduction occurring in some subjects would be consistent with a larger mean predicted than mean observed third TDM levels, as well as with the positive bias in third level predictions. It must also be noted that day-to-day assay variation was greatest for digoxin and carbamazepine with coefficients of variation of 14.4 percent and 7.5 percent, respectively. It is likely that the higher assay noise for these drugs was also reflected in the outcomes.

Pharmatrol-based third level predictions appeared to be reasonably precise and relatively unbiased, particularly in light of the prevailing conditions under which predictions were made. First, data entry was based upon the assumption that charted dosing histories were correct. Clearly this assumption is not universally valid. In fact, for AG infusions both for adults and geriatric patients the duration was assumed to be 30 min. However, no instance could be found in which the actual infusion period was, in fact, noted. Thus, some robustness to errant assumptions about dosing history seems to reside in the program. Second, a fairly unconstrained sequence of sampling times was operated upon for calculation of pharmacokinetic parameters. The first two TDM levels upon which calculations were based for the drugs reported herein represented a mix of mid-dose and trough samples. For AG drugs putative peak plasma levels were also used. Moreover both pre-steady-state, steady-state, and mixes of pre- and steady-state levels were used.

Third, a diverse group of patients was accommodated by these computer-based calculations. Not only was there diversity in our patient material regarding age and weight, but also in terms of general health. Patients with extreme variations in renal and liver function were among our sample. In that connection, it must be emphasized that mean CL values reported cannot be construed to represent population means. That will only be possible when data have been accumulated from sufficient numbers of patients representing distinct subpopulations (e.g., neonate, geriatric, renal failure, etc.).

Fourth, these analyses were performed without regard to possible changes in patients' pharmacokinetic stability. That is, in some cases the three TDM levels embraced historically distinct times in a patient's stay, e.g., before, soon after, and long after a procedure such as surgery. Similarly, since the pharmacokinetic analyses were performed in the course of routine TDM and routine care, most patients were receiving multiple medications in addition to those of TDM interest. Finally,
both intravenous and oral routes of administration were accommodated, and in the case of orally administered drugs multiple formulations were accommodated.

Pharmatrol appears to represent one of several new microcomputer-based approaches for estimating individualized pharmacokinetic parameters which can operate with limited TDM data collected within the constraints and exigencies of usual patient care. The accuracy of those estimates was reflected only in the accuracy with which future TDM levels were forecast.

Armed with patient-specific pharmacokinetic constants, it should be possible to tailor more closely drug dosages to an individual patient's requirements. Other computer-based calculations also afford flexibility, robustness, and precision. Such programs have been shown to estimate effectively pertinent pharmacokinetic parameters for AGs, digoxin, lidocaine, and phenytoin. Accurate estimation of computer-simulated theophylline kinetic parameters has also been demonstrated. Other strategies for estimating pharmacokinetic constants from limited data have been implemented successfully. A software system for individualizing AG doses has been described. Both Chiou's method for theophylline and the peak/trough method for AGs do not require software, although the methods may be implemented on microcomputers. Ball's computer-based estimates of AG and theophylline kinetic parameters implemented on an Apple computer are calculated by an ordinary least squares technique.

The basis for invoking computer-based strategies to estimate individualized pharmacokinetic parameters is to permit the construction of optimal, patient-specific dosage regimens early in therapy so that a patient can rapidly be brought to a safe and effective plasma drug concentration with a minimum of further dosage refinements required thereafter. Apart from increasing the effectiveness and decreasing the morbidity of drug therapy for those drugs with narrow therapeutic indices, the contribution of lengthy dosage titrations to the length of hospital stay should be diminished. Preliminary reports indicate that this will likely be so. Pharmacokinetically adjusted AG regimens were about four days shorter, and patients receiving pharmacokinetically-structured AG doses showed clear roentgenograms some 13 days prior to their non-pharmacokinetically dosed counterparts. Length of stay was eight days shorter for the pharmacokinetically dosed patients and the mortality rate was one-third that of non-pharmacokinetically dosed patients. Similarly, Mungall et al have shown that (1) implementation of pharmacokinetically-based theophylline dosages shortened the time required to stabilize patients on oral medication by three days, (2) length of stay in intensive care was reduced by five days, and (3) hospital stays were reduced by seven days compared to patients whose doses were not pharmacokinetically structured. Clearly staged studies of existing and developing software aimed at refining drug dosing strategies through better use of TDM data are warranted. Not only must such systems demonstrate an ability to estimate effectively individual pharmacokinetic constants, but their effectiveness in improving patient management must be evaluated as well. Moreover, studies comparing the effectiveness of different systems or programs are needed.

In the current climate of health care cost containment, the application of computer-based pharmacokinetic structuring of drug dosages based on limited
TDM data holds some promise, and the impact of such strategies warrants continued investigation.

Acknowledgments

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References