IMPROVED 2-COMPARTMENT TIME-SHARED PROGRAMS FOR ADAPTIVE CONTROL OF DIGITOXIN AND DIGOXIN THERAPY

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Abstract

Computer programs for adaptive control of digitoxin and digoxin therapy have been developed using a 2-compartment pharmacokinetic model. The amount of drug in the peripheral compartment correlates with inotropic effect of the drug. Therapeutic goals are stated as a desired peak total body glycoside concentration (μg/kg body weight) in the peripheral compartment. Dosage regimens are computed to achieve and maintain this goal. Serum levels can be obtained at any time after a dose. The model can be fitted to serum data using a maximum a posteriori probability Bayesian procedure.

Introduction

The clinical effect of cardiac glycosides correlates poorly with data of serum levels until at least eight hours after a dose have elapsed and distribution of the drug has taken place. Clinicians have avoided obtaining serum levels for therapeutic drug monitoring until after the distribution phase. Usually, levels have been obtained only just before the daily dose is given. Little information about the dynamic events occurring with cardiac glycoside therapy is obtained. Such management of digitalis is logically equivalent to managing aminoglycoside therapy by obtaining only trough levels. It is not surprising that most clinicians have not found serum glycoside levels as helpful for monitoring and adjusting digitalis therapy as for aminoglycoside therapy.

However, multi-compartment pharmacokinetic models of digitoxin and digoxin kinetics and dynamics have been made. The analysis of Reuning, Sams, and Notari, clearly shows that serum levels are well fitted by a 2-compartment model, and the rise and fall of computed amounts of drug in the peripheral compartment correlate well with changes in the inotropic effect of digitoxin. Similarly, a previous study of the bioavailability of digitoxin in our laboratory also yielded a multi-compartment model. The rise and fall of the computed amount of drug in the peripheral compartment was consistent with the known clinical behavior of digitoxin and its known time to peak effect.

Two Compartment Computer Programs for Digitalis Therapy

Our laboratory has now developed computer programs for planning, monitoring, and adjusting digitoxin and digoxin therapy using these above pharmacokinetic models. Data of past dosage and serum levels may be entered and the pharmacokinetic model fitted to the serum data. Either least squares of M.A.P. (Maximum A posteriori Probability) Bayesian fitting procedures may be used. The fitted model is then used to reconstruct the time course of serum levels and peripheral compartment total body concentrations (μg of glycoside per kg of body weight), over the patient's past therapy. One can evaluate which computed peripheral total body glycoside concentrations are associated with desired clinical responses to therapy and which are not. One can choose a therapeutic goal in the form of a desired peripheral compartment body glycoside concentration.

Note that these computer programs do not compute doses to achieve and maintain desired serum levels. Instead, the goal of therapy is expressed as a desired peak total body glycoside concentration in the peripheral compartment, in μg/kg. A dosage regimen is computed to achieve and maintain this goal. In earlier versions of the program, doses were computed to achieve and maintain desired peak serum levels. However, a significant lag in equilibration of the peripheral compartment was found, which required four to five days for full equilibration to take place. Because of this, it was decided to change the therapeutic goal from a desired serum concentration to a desired peak total body glycoside concentration in the peripheral compartment. The programs now compute a dosage regimen to achieve and maintain that goal, using the oral route. If intravenous therapy is contemplated, 65% (the assumed bioavailability fraction) of an oral dosage regimen is given as a 15 minute intravenous infusion (80% for digitoxin).

Following computation of the oral regimen, the program then provides the ability to revise this so that conventional tablets may be used. In addition, it provides a "standard revised format" which allows the user to divide the loading dose into 2 or 3 parts each 6 hours apart. The program then asks him what size tablets he wishes to use, and expresses the total loading dose as the total number of such tablets. The operator enters how many of these tablets he wishes to put into the first, second, and third portion of the loading dose. Following this, the maintenance dose is computed for an average entire week of therapy and the program apportions this total weekly dose into so many...
tablets so many days a week and a different number of tablets for other days of the week.

The program to date has been useful in several ways. It permits a serum level to be obtained at any time. There is no need to wait until 8 hrs after a dose before obtaining a serum level. Indeed, considerations of optimal sampling strategy for a 2-compartment model strongly suggest that the primary goal of monitoring serum levels now becomes that of characterizing the volume of distribution and the elimination rate constant for the patient's central compartment. Because of this, it is desirable to obtain a peak serum level after an oral dose at about 1.5 to 2 hours after such a dose, as this provides the most accurate information concerning the apparent volume of distribution of the central compartment. If a glycoside is given intravenously as a 15 minute infusion, then the peak serum level is best obtained from the opposite arm at the end of the infusion. Information concerning the elimination rate constant is best obtained with a trough serum level just before a subsequent dose, and by delaying obtaining this until the latest possible dose interval consistent with the clinical urgency. If it is desired to obtain further information concerning the rate constants and from the peripheral compartment, preliminary calculations suggest that two other levels might be obtained; one at one-half hour after a dose and the other at 7 hours after a dose.

These 2-compartment programs provide the user with an extended capability to monitor serum levels intelligently, using established mathematical concepts, and to react to them intelligently, developing a useful reconstruction of the time course of past therapy in both the central and peripheral compartments, for comparison with the patient's clinical behavior over that entire time; and the ability to develop dosage regimens, taking into account not only the data of serum levels that one has found in the past, but also the considerations of optimal sampling strategy for a 2-compartment model strongly suggest that the primary goal of monitoring serum levels now becomes that of characterizing the volume of distribution and the elimination rate constant for the patient's central compartment. Because of this, it is desirable to obtain a peak serum level after an oral dose at about 1.5 to 2 hours after such a dose, as this provides the most accurate information concerning the apparent volume of distribution of the central compartment. If a glycoside is given intravenously as a 15 minute infusion, then the peak serum level is best obtained from the opposite arm at the end of the infusion. Information concerning the elimination rate constant is best obtained with a trough serum level just before a subsequent dose, and by delaying obtaining this until the latest possible dose interval consistent with the clinical urgency. If it is desired to obtain further information concerning the rate constants and from the peripheral compartment, preliminary calculations suggest that two other levels might be obtained; one at one-half hour after a dose and the other at 7 hours after a dose.

Clinical Experience with the Programs

In addition to providing an improved tool for routine monitoring and adjustment of glycoside levels, the programs have provided interesting insights into two special clinical situations. The first is in the achievement and maintenance of proper control of ventricular rate for patients with atrial fibrillation. The second is for managing cardiac glycoside therapy for patients who must also receive quinidine.

Controlling the Ventricular Rate with Atrial Fibrillation

A 54 year old lady with mitral stenosis and atrial fibrillation had a ventricular rate that was difficult to control with ordinary doses of digoxin. She had low serum levels. Because of this, incremental doses were given every six hours, and 2 pairs of peak and trough serum levels were obtained after two successive doses, in addition to two prior serum levels. The model was fitted to the data, and it was seen that her central volume of distribution and her elimination rate constant were both well above the population mean, as was her rate constant from the central to the peripheral compartment. A therapeutic goal of 13µg/kg was picked. The dosing regimen to achieve this was computed, and the first increment of the loading dose was 7.5µg. This was given a few hours after the concomitant theophylline therapy, which she had received for many days, had been discontinued. As a result of these two things, her ventricular rate then became quite well controlled at 70 per minute. Because of this, the therapeutic goal was revised and the program was re-run with a new therapeutic goal of 11.4µg/kg, which had been reached with that first increment of the loading dose, and which was associated with the ventricular rate of 70/min. The resulting maintenance dosage regimen was .6493mg/day. It was given as .625mg/day 6 days/week and .75mg/day 1 day/week. On this regimen her ventricular rate continued to be quite well-controlled in the general range of 70 to 80. No visible change or slippage in her clinical state of digitalization was detected.

In contrast, after she had received her cardiac surgery, approximately 1 month later, her digoxin was discontinued. She went through a series of arrhythmias, and then finally settled into atrial fibrillation once again, for which she was given digoxin. At this time, however, no serum levels were available for fitting and guidance. Because it was not known whether her digoxin requirements would continue to be the same after surgery as before, a maintenance dose of .5mg/day was intuitively chosen and given. On this regimen, however, her ventricular rate gradually rose to approximately 95. The previous regimen was then re-instituted and her ventricular rate once again reached control. Because of this, it is felt that use of this program to achieve and maintain rate control in patients with atrial fibrillation may often eliminate 2 to 3 days of hospital stay (and possibly more) due to the time currently required to choose and evaluate a maintenance dosage regimen using conventional intuitive techniques.

Managing the Digoxin-Quinidine Interaction

The program also provided new insights in a patient receiving simultaneous digoxin and quinidine. A 52 year old black lady with chronic atrial fibrillation developed chronic atrial flutter with 2:1 AV block following mitral valve replacement in the past. This was not well controlled on .25 of digoxin daily. Quinidine, 300mg 6qH, was added by others, to attempt to slow her atrial (and therefore her ventricular) rate. Her atrial rate slowed and her ventricular rate also slowed somewhat, but good rate control was not achieved despite digoxin levels of 2.2µg/ml trough, 4.9µg/ml 3.5 hours after a dose two doses later, and 2.8µg/ml 23 hours after that same dose. Fitting the 2-compartment model to this data, as shown in Table 1, revealed not only a marked reduction in the volume of distribution of the central compartment, but also a significant increase...
in her elimination rate constant. Despite this, however, the clearance of digoxin from her central compartment (volume x Kel) was markedly reduced, to only 1.97 liters per hour. Her peak total body glycoside concentration in the peripheral compartment was also markedly reduced, to 4.25 ug/kg. The reduced clearance and elevated serum levels were expected and are consistent with the data in the literature. The surprise was the finding that the computed amount of glycoside in her body (both central and peripheral compartments) at trough was only 510 ug, less than half the similar computed amount found later on without concomitant quinidine and with lower serum levels. This finding is consistent with data in the literature which showed reduced uptake of digoxin in most tissues (except the central nervous system) in the presence of quinidine. This unexpected clinical finding, however, strongly suggests that while serum levels were elevated, quinidine may actually have reduced the total amount of digoxin in the body of this patient. This finding is also consistent with the reduced inotropic effect of digoxin which has been found in the presence of quinidine. Because of this, one may perhaps view the peripheral compartment data in this program as reflecting the general relative magnitude of inotropic effect, and the central compartment as reflecting the general relative elevations found in the tissues of the central nervous system. Because of this, the central compartment data might be more related to the incidence and risk of toxicity, while the peripheral compartment data may be more related to relative inotropic effect. The programs thus provide an improved tool to appraise risk-benefit relationships in such clinical situations, and help to manage patients with the interesting clinical problem of the digitalis-quinidine interaction.

**Digitoxin versus Digoxin**

It has been interesting to examine the degree to which the two pharmacokinetic models, one of digoxin, the other of digitoxin, are perturbed by a change in renal function without concomitant adjustment of dosage, and the manner in which the resulting cumulation may lead to clinical digitalis toxicity.

Examination of the behavior of digitoxin and digoxin under such circumstances, using the pharmacokinetic models in this program, has confirmed the smaller and slower accumulation of digitoxin in such circumstances, and its decreased renal sensitivity. Because of this, toxicity develops more slowly with digitoxin therapy and therefore tends to be detected in an earlier stage of its development (at equal observation intervals) when it constitutes less of a threat to life. These pharmacokinetic results confirm those found with a previous 1-compartment model and again suggest that digitoxin may be the preferred glycoside for general use, because of (rather than in spite of) its longer half-time, which confers greater stability upon the total amount of digitoxin in the body in the face of the usual changes in plasma volume and renal function which probably take place in all patients from day to day.

These 2-compartment programs for digitoxin and digoxin therapy are currently in use by several hospitals over an international timesharing facility*. They are highly conversational and are designed for easy use by physicians, pharmacists, and nurses without any previous computer experience.

**References**


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**TABLE 1 - EFFECT OF QUINIDINE UPON PATIENT'S 2-COMPARTMENT DIGOXIN MODEL.**

<table>
<thead>
<tr>
<th>Compartment</th>
<th>A-Priori</th>
<th>D &amp; Q</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vc (L)</td>
<td>99.47</td>
<td>18.301</td>
<td>117.27</td>
</tr>
<tr>
<td>Kel (hr⁻¹)</td>
<td>0.000451</td>
<td>0.001335</td>
<td>0.000244</td>
</tr>
<tr>
<td>Kint (hr⁻¹)</td>
<td>0.028689</td>
<td>NF</td>
<td>NF</td>
</tr>
<tr>
<td>Kcp (hr⁻¹)</td>
<td>0.56</td>
<td>NF</td>
<td>NF</td>
</tr>
<tr>
<td>Kpc (hr⁻¹)</td>
<td>0.15</td>
<td>NF</td>
<td>NF</td>
</tr>
<tr>
<td>Kel (hr⁻¹)</td>
<td>0.0555</td>
<td>0.1070</td>
<td>0.0437</td>
</tr>
<tr>
<td>Clearance</td>
<td>5.181L/hr</td>
<td>1.969L/hr</td>
<td>5.122L/hr</td>
</tr>
<tr>
<td>Calc. peak peripheral conc. (ug/kg, observed/expected)</td>
<td>4.25/7.7</td>
<td>18.75/15.79</td>
<td></td>
</tr>
<tr>
<td>Calc. total Amt in Body (%)</td>
<td>100%</td>
<td>55%</td>
<td>118%</td>
</tr>
</tbody>
</table>

**Vc** = Apparent volume, central compartment

**Kel** = slope of renal component of Kel, with respect to creatinine clearance

**Kint** = non-renal component of Kel

**Kcp** = rate constant, central to peripheral cmpt.

**Kpc** = rate constant, peripheral to central cmpt.

**Kel** = rate constant, elimination, **Kel** = **Kint** + (**Kel** x Creatinine Clearance)

**Clearance** = **Kel** x **Vc**

**D & Q** = Digoxin and Quinidine

**Q** = Quinidine

**NF** = Not fitted.

These programs deal with therapy with digitalis glycosides, lidocaine, aminoglycoside antibiotics, procainamide, and quinidine. The computer programs adjust an initial pharmacokinetic model to important clinical characteristics about that patient. A selected therapeutic goal is entered and a dosage regimen is developed to achieve and maintain it.

In addition, past therapy can be entered, as well as data of serum levels observed on past dosage regimens. This data can then be fitted using M.A.P. (Maximum A-posteriori Probability) Bayesian procedures, to develop an individualized patient-specific pharmacokinetic model. These programs are designed to function in the presence of changing renal function or of changing cardiac output. Because of this, it is not necessary to discard old data and to start all over again. Instead, a laboratory result usually remains viable for the patient's entire hospital admission permitting one to be much more selective in ordering subsequent serum levels. Using this patient-specific model, the time course of past events is reconstructed for comparison and plotted for comparison of the patient's clinical behavior during the past. In this way, the therapeutic situation can be examined and therapeutic goals arrived at.

The programs then develop the dosage regimens to achieve these goals, including interfacing with automated apparatus to deliver these regimens (often involving carefully tapering infusion protocols) automatically, with increased reliability and safety, compared to manually setting and resetting the apparatus. Lastly, the programs compute the optimum times to obtain subsequent blood samples for therapeutic drug monitoring within the confines of clinical constraints concerning urgency and laboratory operating schedules, so that the most efficient and cost-effective monitoring strategies are utilized.

These programs have increased the precision and efficacy of therapy for a number of these drugs in several hospitals where they have been used. They can be run on an internationally available timesharing facility.*

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