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Some Comments and Suggestions concerning Population Pharmacokinetic Modeling, especially of Digoxin, Monitoring its Therapy with Serum Concentrations, and Optimizing its Clinical Dosage Regimens

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Some Comments and Suggestions concerning Population Pharmacokinetic (PK) Modeling, especially of Digoxin, Monitoring its Therapy with Serum Concentrations, and Optimizing its Clinical Dosage Regimens

ABSTRACT

Population PK modeling is often performed upon data of steady state trough serum concentrations, in the course of “routine” therapeutic drug monitoring (TDM). This design is extremely uninformative, and permits only estimation of a single parameter of a 1 compartment model, such as clearance. Use of D-optimal design strategies permits much more information to be obtained, with models of much more meaningful structure. Strategies for routine TDM policies need to be optimized, incorporating these principles.

Software for population PK modeling has been dominated by NONMEM. However, since NONMEM is a parametric method, it must assume a shape for the model parameter distributions. If the assumption is not correct, the model may well be in error. In addition, the likelihood function computed by NONMEM is only approximate, not exact. This impairs statistical consistency, efficiency, and precision of parameter estimates. Other parametric methods now available are better, with exact likelihoods, but still suffer from having to assume what the shape of the model parameter distributions is supposed to be.

Nonparametric (NP) methods appear to be better. They do not have to make any assumptions about the shape of the parameter distributions. They have exact likelihoods, are statistically consistent, efficient, and precise. They also permit maximally precise dosage regimens to be developed for patients using multiple model (MM) dosage design, something parametric modeling methods cannot do.

Laboratory assay errors are better described by the reciprocal of the assay variance of each measurement rather than by their coefficient of variation. This is easy to do and permits more precise models to be made. This also permits separate estimation of the other sources of noise in the clinical environment, which is most useful.

Digoxin has at least 2 compartment behavior. Its pharmacologic and clinical effects (both therapeutic and toxic) correlate not with serum digoxin concentrations, but with those in the peripheral nonserum compartment. Some illustrative examples of this are discussed.

Investigators have often used steady state trough concentrations only to make a 1 compartment model, and have only sought to predict future steady state trough

concentrations. Much more can be done, and clinical care can be much improved. Further work along these lines is greatly to be desired.

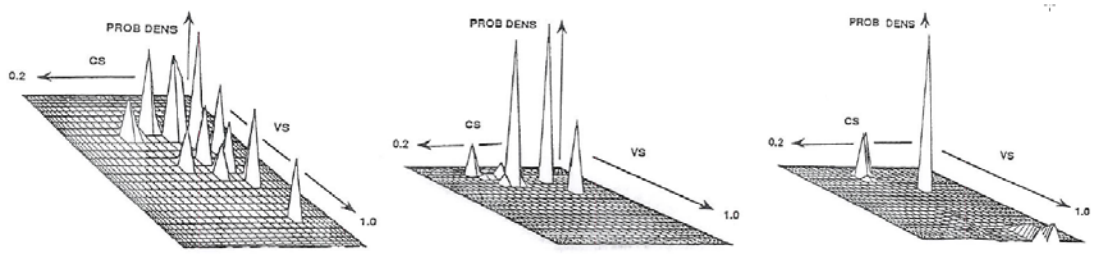
POPULATION MODELING BASED ON ”ROUTINE” DATA FROM THERAPEUTIC DRUG MONITORING (TDM).

Investigators not uncommonly perform population studies of drug behavior in patients by using data of “routine” therapeutic drug monitoring (TDM). This frequently uses data of trough serum drug concentrations drawn in the steady state. In addition, the goal of such studies often is also only to predict similar steady state trough concentrations in the future.

I would like to offer come comments and suggestions about this strategy, especially as it pertains to population modeling of digoxin, the use of serum digoxin measurements in modeling both the clinical as well as the pharmacokinetic and dynamic (PK/PD) behavior of the drug, and the utility of therapeutic drug monitoring combined with software employing nonparametric (NP) population models and multiple model (MM) dosage design for the optimization of digoxin therapy.

1. Investigators often use data of “routine” trough serum digoxin concentrations measured only at a steady state, and made the only model possible from that data, namely a 1 compartment model. The absorption rate constant and apparent volume of distribution are often fixed at literature values. The only parameter estimated may be clearance. The goal of the study is often restricted only to the prediction of similar steady state trough serum concentrations in the future, which they may do well enough.
2. The illusion, apparently held by many, is that one can make meaningful population pharmacokinetic (PK) models from such steady state “routine” data. It is simply not possible to do so. No model having any real structure can be made from such minimally informative data. The rationale usually offered for such lack of concern for experimental design is that as long as the total number of data points is greater than the number of model parameters, then population modeling “will work”.
3. An example of the crucial role of experimental design is shown in Figure 1, taken from [1]. Figure 1A shows the results obtained from a nonparametric population analysis [2] of data from the full dataset of 177 patient serum concentrations obtained at various times after a dose in 20 patients receiving repeated doses of gentamicin, using a 1 – compartment PK model. Figure 1B shows the degraded results obtained from restricting the dataset to 40 measurements, 2 samples per patient, the highest peak and the lowest trough. Figure 1C shows the still more degraded results obtained by

restricting the samples to 20, sampling only the single lowest trough from each patient. The figure shows that the protocol used in obtaining data from which a population PK model is made has a truly profound effect upon the modeling results obtained.



1A 1B 1C

Figure 1A, left, shows the NP estimated density of clearance slope (CS) per unit of creatinine clearance (ml/min/1.73 M2, horizontal axis), volume slope (l/kg, downward and rightward axis), and probability (vertical axis). The vertical spikes are the discrete nonparametric support points which constitute the estimated entire model (1 compartment) parameter distributions. Results obtained from the full dataset of 177 measured concentrations in 20 patients.

Figure 1B, center, shows the much different parameter estimates, based only on the pair of the highest peak and lowest trough from each patient. Note the degraded results. Axes as in 1A.

Figure 1C, right, shows the even worse results when the dataset is restricted to only the single lowest trough sample from each patient. Axes as in 1A.

4. One might look at [3] for a good discussion of the issues of optimal experimental design for guiding pharmacokinetic experiments, and of managing TDM in general. Use of optimal design strategies can greatly increase the capability of any PK study and also of policies for routine TDM. They will permit making rather a population or an individual model of a drug in a patient that has real structure to it. For TDM of digoxin, which has a highly significant peripheral nonserum compartment [4], I would suggest drawing serum samples at times close to the D-optimal times - a peak serum sample drawn either 5 min after a 15 min intravenous infusion, or 1.5 hours after an oral dose, and a trough. In addition, it is often useful, I think, to supplement them with measurements taken 0.5 hour and 7 hours after a dose (by either route) to best estimate the rate constants from the central out to the peripheral compartment and back again [5]. In managing patients, I have at times obtained not only a peak and trough pair in one dose interval, but also the other pair in another, for example, going back and forth if needed.
5. One reason that monitoring trough serum drug concentrations has been so popular is that the effects upon the measurement of the errors made in

recording the times of dose administration and of drawing the blood are minimized. However, the result is that information of drug behavior over time is also minimized, and the least informative sample has actually been selected. Without dynamic information obtained by good experimental design, as in [3], no meaningful PK or PK/PD model can be made without much richer data. This is another way of saying that it is also crucial to record accurately the times at which doses are given and serum samples are drawn. Also, in general, one needs to get, at a minimum, over several dose intervals if needed, at least 1 sample for each model parameter to be estimated, either for a PK study or for good TDM protocol.

6. Drug companies often use D-optimal design to make population models, as they get better information from fewer patients at less cost. For example, they may start by studying about 5 patients using an initial protocol, and then make a population model based on those 5 patients. Then they may use optimal design strategies to optimize the sampling protocol for several more patients. They may iterate this process until the sampling strategy becomes stable, and they have developed the best model (out of several candidate models) from sampling the fewest patients, thus getting the most value from the dollars spent on the study.

SOFTWARE FOR POPULATION MODELING

1. NONMEM [6] has probably been the most widely used population modeling method. It is a parametric method. As such, it must assume the shape of the distribution of the model parameters, such as normal, lognormal, or perhaps bimodal. Some distributions, such as lognormal, may well be chosen for statistical convenience, avoiding negative parameter values in the distribution. The NONMEM parameter estimates obtained are single point estimates of the model parameter means, variances, and covariances. However, parametric methods cannot estimate the entire parameter distributions, as is done by the more capable nonparametric methods [2,7-9]. When one uses a parametric model to develop a dosage regimen to hit a desired therapeutic target goal, the separation principle [10] states that the task is done suboptimally, as there is no performance index available to evaluate and optimize the expected precision with which the target will be hit, as information from the full model parameter distributions is not available. One simply develops a regimen designed to hit a desired target goal exactly, and knows that it will not.
2. Further, the likelihoods computed by NONMEM are not exact, but only approximate (the FO, FOCE, and similar algorithms). Because of this, results are often in error (often only about 2% for means, but about 30% for

variances, and really gross for correlations). Also, because of its FOCE approximation, there is no mathematical guarantee that if one studies more patients, the estimated parameter values will approach the true ones more closely [2,7-8]. In short, there is no guarantee of statistical consistency. Other parametric methods, however, do have exact likelihoods, and do have the guarantee of statistical consistency [11-12]. However, they still have the significant limitation resulting from having to assume the shape of the model parameter distributions, and of only obtaining single point estimates of them.

3. Instead of only estimating parameter means and covariances of the assumed distributions, as is done by parametric methods, nonparametric (NP) modeling methods [2,7-9] estimate the entire parameter distributions themselves. They obtain a discrete distribution, based on the theorems of Caratheodory, Lindsay, and Mallet [2,7,13]. The NP model parameter distributions consist of multiple discrete points (support points), up to 1 per patient studied in the population. In addition, the likelihoods are exact, and statistical consistency is assured. Each discrete support point consists of an estimated value for each model parameter, and an estimate of the probability of that point in the population. Model subpopulations such as fast and slow metabolizers are easily recognized without further effort.
4. There has recently been a “nonparametric” option implemented in NONMEM [14,15]. For the location of the support points, however, this option uses only the maximum aposteriori probability (MAP) Bayesian posterior values of the individual subjects studied, and then computes their probability. This leads to significant mislocation of the support points, as shown by Leary et al [16], and is notably inferior in performance to the more rigorous methods discussed above [2,7-9].

MULTPLE MODEL DOSAGE DESIGN

1. The multiple support points in the rigorous NP population models obtained by estimating the entire parameter distributions permit multiple predictions of future serum concentrations and other responses. As a candidate regimen is presented to each population model support point, each support point prediction is weighted by its estimated probability. It is easy to calculate the weighted squared error with which any dosage regimen fails to hit the desired therapeutic target goal at the desired time. This optimization process then continues until the regimen is found which specifically minimizes that expected weighted squared error. In this way one develops the regimen that now hits the target with maximum precision. This is known as “multiple model” (MM) dosage design [17-19]. MM design and Bayesian adaptive control is well

known and widely used in the aerospace community for flight control and spacecraft guidance systems. One cannot control a system merely by "Bayesian forecasting". It requires control. Our MM-USCPACK software [19] uses NP population modeling and MM dosage design to obtain maximally precise dosage regimens, and also uses MM Bayesian adaptive control. That cannot be done using parametric models. It is the combination of NP modeling, and MM maximally precise Bayesian adaptive control, rather than the less capable MAP Bayesian adaptive control. MM Bayesian adaptive control permits dosage regimens, individualized for each patient, to hit with maximum precision a specific target goal selected for each patient according to his/her perceived clinical need for the drug, including, for digoxin, a clinically selected target in either the central (serum) or in the peripheral (nonserum) compartment. MM Bayesian adaptive control is widely used in the aerospace community for flight control and spacecraft guidance systems.

2. I would respectfully suggest that instead of merely using a population modeling method with which to do a study, simply because it is available, that investigators should now examine the real capabilities of the many methods now available, both parametric and nonparametric, which have exact (rather than only approximate) calculations of the likelihood function, and that investigators justify in their work the specific reasons why they select a particular population modeling method to use in their studies.

ANALYSIS OF ERRORS

1. Weighting schemes used in fitting models to data have, as everyone knows, a most significant effect on the results obtained. It is often assumed that the drug assay error is only a small part of the total error involved in doing a study. If one does as many investigators do, examining various overall error models and then estimating parameter values of the model giving the best fit, one will never know how much of the overall error is due to the assay, and how much is due to the other clinical environmental factors, such as the errors in preparing and giving the doses, errors in recording the times of doses and of drawing the blood samples, model mis-specification, and possible changing parameter values during the period of data analysis. The real information of the assay error itself is all too often discarded once it is shown to be "acceptably precise".
2. Instead of using CV%, one can first determine the error of the assay itself, expressed not as the percent coefficient of variation (CV%) but as the reciprocal of the assay variance at any measured concentration [20,21]. One has to get the standard deviation (SD) first anyway in order to get the CV%.

3. If one gets the SD, squares it to get the variance, and weights each measurement by the reciprocal of its variance, then one also does not need to censor low measured concentration results having an "unacceptably high" CV% [21]. There are many assays such as HIV, HCV, and HBV assays, which, in addition to drug concentrations, one does not want at all to censor low values, but instead to drive them to zero, into the machine noise (where the assay CV% is infinite), and to document this fact. Giving correct weight to the measured concentrations insures a model with maximally precise parameter values and distributions. This can be done easily and cost-effectively by determining the assay SD as a polynomial function of the measured value [21]. The remaining error due to the environmental factors can easily be estimated separately from the previously determined assay error polynomial which is described in [21].
4. For example, one can estimate gamma, in the MM-USCPACK and its new Pmetrics population modeling software [22]. Gamma is a proportional error term. If gamma is 2.0, it means that the total noise, assay plus environmental, is twice the assay error. If so, one can be comforted, as the environmental error is small. On the other hand, if gamma is 10.0, for example, it reveals considerable noise in the clinical part of the study, and one may wish to take steps to make that part of the study more precise. If desired, one can now choose to estimate an additive term which we call lambda, instead of the multiplicative term gamma. This is probably a better strategy than estimating gamma, as it does not multiply up the usual curvature present in the assay error polynomial.

<u>MODELING DIGOXIN</u>.

1. The most common clinical study of digoxin PK has been to use a 1 compartment model. However, Reuning et al [4] and others [23-27] clearly showed as far back as 1973 that digoxin has at least 2 compartment behavior, and, most significantly, that the pharmacological effect of the drug correlates, not with serum concentrations, but rather with drug amounts in the nonobservable but easily calculable peripheral nonserum compartment [4]. Their work appears to have gone essentially unnoticed.
2. Our group at the USC Laboratory of Applied Pharmacokinetics made an adult population model based upon the work of Reuning et al, and estimated the concentrations in the peripheral compartment (ug/kg body weight) from standard dosage regimens in so-called "average" patients, as well as the D-optimal times to obtain samples, as described earlier above. We developed software to calculate dosage regimens of digoxin to achieve selected target

concentration goals at target times either in the serum or in the peripheral compartment. For trough serum concentrations of about 0.9-1.0 ng/ml, conventional dosage regimens of about 250 ug/day largely achieve these goals when renal function is normal, and one can see that the peak peripheral concentrations are about 7 ug/kg [5]. This model has worked extremely well clinically in our hands for patients in regular sinus rhythm.

DIGOXIN SERUM CONCENTRATIONS

1. "Therapeutic" serum digoxin concentrations are often said to range from about 0.5 to 2.0 ng/ml, and most patients in regular sinus rhythm (RSR) do well with trough serum concentrations of about 0.9 ng/ml. Most patients with toxicity have serum concentrations over 2.0 ng/ml. However, it is also well shown that quite a few patients tolerate serum digoxin concentrations well over 3 ng/ml, and actually as high as 7 ng/ml without toxicity [28]. In addition, patients with atrial fibrillation (AF) who have good atrioventricular nodal conduction often require serum concentrations of 2.0 ng/ml for adequate control of ventricular rate [29,30]. Others have commented on the inadequacy of "therapeutic" serum concentrations to get good rate control in AF [31]. However, it seems not to have been considered by most cardiologists that patients with AF might require their own separate "therapeutic ranges".
2. Rigid use of "therapeutic ranges" neglects the great variation in sensitivity of individual patients to digoxin, or to any drug. Again, as Doherty has shown [28], patients may tolerate serum concentrations up to 7.0 ng/ml without toxicity. I have seen one patient with atrial fibrillation (AF) who required a serum concentration of 8.0 ng/ml for adequate ventricular rate control, (without toxicity) [5], and a colleague has also had a similar patient who required 6.0 ng/ml to do the same job [32]. This great variation in sensitivity, probably due to genetic polymorphism in setting the binding constant of digoxin to membrane Na – K ATPase, seems to have been forgotten by many clinicians, who are taught to live in awe of the so – called "therapeutic ranges". One needs, I think, to accept rather than evade one's clinical responsibility, and to accept the fact that one must "look at the individual patient", who will then tell the clinician, by his/her clinical behavior, what serum or peripheral compartment digoxin concentration is best. The concentration of drug in the serum never helped or hurt anyone. As shown by Reuning et al, it is what is in the tissue or on the cell membrane (even the red blood cell) that has both the therapeutic, and probably also, its toxic effects.

3. Digoxin acts by competing with potassium for binding sites on the cell membrane Na –K ATPase. Inward flow of K is slowed. The cell loses K, gains Na, and through exchange with Na – Ca ATPase, the cell gains Ca. It is the greater availability of Ca that results in the increased inotropic effect of digoxin. In addition, just about all the manifestations of digitalis toxicity are seen as well in patients with hypercalcemia from any cause – the anorexia, nausea, vomiting, arrhythmias, delirium, and psychoses. The visual symptoms with digoxin may well be due to retinal cell ectopic activity, where they may fire several times when stimulated rather than only once. The released visual pigment diffuses to surrounding areas and alters the color perception of adjacent retinal cells. In this way, it is my speculation that digitalis compounds may well facilitate the formation of <u>afterimages</u> in the retina, thus causing the many and varied visual symptoms.

<u>DIGOXIN IN ATRIAL FIBRILLATION</u>

1. In addition to treating patients with RSR in a stable steady state, there are also rapidly evolving clinical situations when one does not wish simply to achieve a final steady state target serum concentration goal. It is often clinically imperative to achieve and maintain a selected target concentration quite rapidly, especially in the peripheral compartment, as when one wishes to obtain good control of ventricular rate in patients with atrial fibrillation or flutter, or perhaps even to convert such a patient to sinus rhythm. After obtaining successful conversion, it is then imperative right then to calculate the proper dosage regimen to maintain the selected target goal after conversion has been obtained. This “best next move” after obtaining successful conversion is what is all too often not possible without guidance by models and software.
2. It is apparently “well known” in the literature that digoxin is no better than placebo for converting patients with atrial fibrillation to sinus rhythm. The study by Falk et al, for example, purports to have shown this [33]. The problem is that the study was extremely underpowered, to the extent that it was basically impossible to detect any significant difference between the study and the placebo arms. There were only 18 patients in the study arm, and the same in the control arm. Further, they gave digoxin only in the form of a fixed protocol, rather than by using standard clinical titration, and did not report the age, weight, or renal function of their patients. Eight of 18 placebo patients spontaneously converted, compared with 9 of 18 in the digoxin arm. Actually, it appears that they did not give enough digoxin to do the job, as we will see below.
3. If one assumes a 65 year old man, 70 inches tall, weighing 70 kg, with a serum creatinine of 1.0 mg/dL, his estimated creatinine clearance [34] is 69ml/min/1.73

M^2. If one gives the digoxin protocol of Falk et al, giving 0.6 mg orally at first, then 0.4 mg at 4 hours, followed by 0.2 mg at 8 hours, and finally 0.2 mg at 14 hours, Figure 2 (thick black line) shows the trajectory of the weighted average estimated serum concentrations over the first 24 hours. The highest is 1.8 ng/ml, and the final concentration is 1.3 ng/ml.

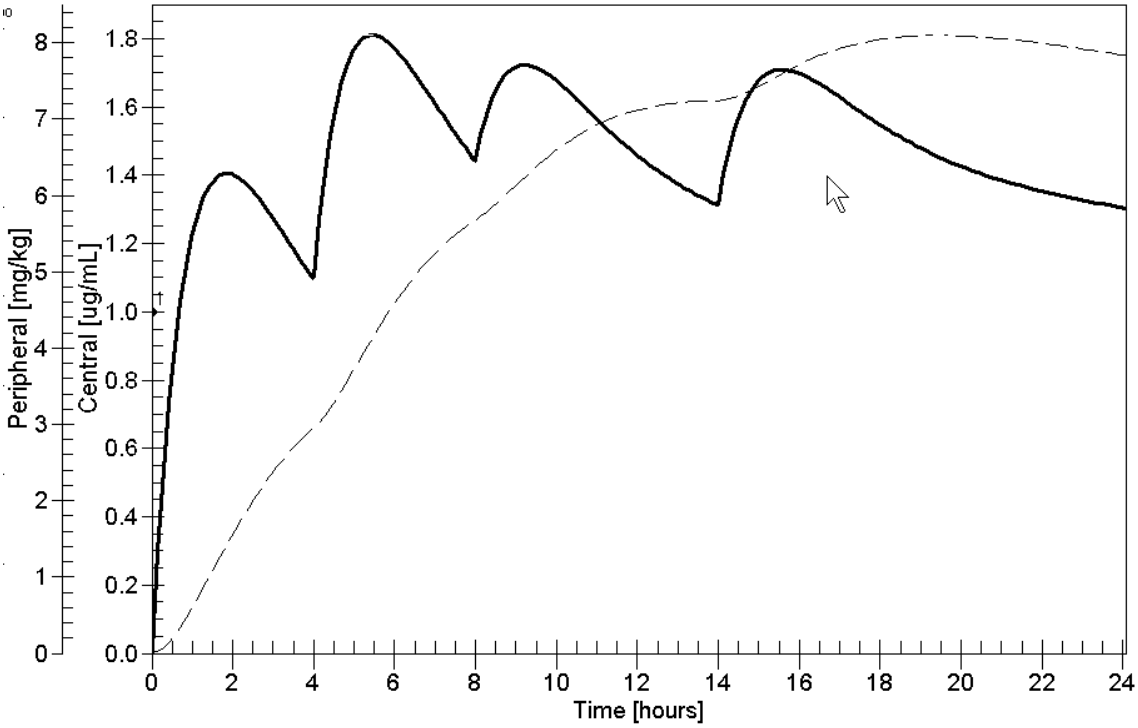


Figure 2. Plot of estimated serum concentration profile (thick black line) and peripheral compartment profile (dashed line) over 24 hours when the regimen given by Falk et al [33] is given to the patient described above. All values are in the range useful for patients with RSR. No clear relationship between doses, serum concentrations, and clinical response is seen from the serum concentration profile. Note that peripheral concentrations correlate well with the additive effect of each dose, but rise only to 8 ug/kg, only a little above the 7 ug/kg at which most patients in RSR do well. Vertical axis: central serum concentrations in ng/ml, NOT ug/ml as shown. Peripheral compartment concentrations in ug/kg, NOT mg/kg as shown. Horizontal axis: hours into the regimen.

4. Figure 2 also shows the time course of the estimated digoxin concentrations in the peripheral nonserum compartment, based on [4]. The highest concentration was 8.0ug/kg, only a little higher than the 7.0 ug/kg which is associated with reasonable therapy for patients in congestive failure with RSR, and with a trough serum concentration of 0.9 – 1.0 ng/ml.
5. In contrast, I have been involved with three patients in whom conversion to sinus rhythm was achieved by careful clinical titration, out of four. The rate

was well controlled in the fourth, who was also hyperthyroid. Their calculated peripheral compartment digoxin concentrations' ranged from 9.5 to 18 ug/kg.

6. An illustrative clinical example was discussed in [21], when a patient with new onset atrial fibrillation was converted three times with titrated doses of digoxin, only to revert twice because an adequate maintenance dose was not given until after the situation was analyzed with our software and an appropriate maintenance dosage regimen was developed. Finding the correct maintenance dose without such models is a real problem clinically because the relationships between doses, serum concentrations, and peripheral compartment concentrations cannot be seen or evaluated quantitatively. Models and software are required.
7. Figure 3 below analyzes the data of the patient described in [21]. This was a telephone consultation with William Nicholson, M.D., when he was a cardiology fellow at Stanford. In this example, a 58 year old man, 68 in tall, weighing 75 kg, with a stable serum creatinine of 0.8 mg/dL, was in a steady state with regular sinus rhythm (RSR) on chronic oral digoxin maintenance therapy of 0.25 mg/day. However, the patent missed a dose one day, and developed new onset rapid AF. He was titrated with several IV doses of digoxin, while being observed for control of his ventricular rate, development of toxicity, or possible conversion to regular sinus rhythm (RSR). After 4 IV doses of 0.25 mg each, given over 1 day, he converted to RSR.
8. The clinical problem then was what dosage regimen to give him to keep him in the RSR that had again been achieved. His previous maintenance dose of 0.25 mg/day was again given, as it was not clear whether his requirements for digoxin had changed or not. He excreted his extra digoxin, and went back into AF after two days. At this point they obtained a serum digoxin sample, taken 11 hours and 15 minutes after the last dose. It was 1.0 ng/ml, and the patient was in AF at that time. The patient was again titrated with extra IV digoxin. He again converted to RSR, this time after only two IV doses of 0.25 mg given three hours apart. A serum sample was obtained 14 hours 20 minutes after the most recent dose, when he was in RSR. The concentration, surprisingly, was exactly the same – 1.0 ng/ml.
9. The question was - how can someone be in AF at one time and in RSR at another time and have exactly the same serum concentration? It is well known that serum digoxin concentrations may not correlate at all well with clinical behavior. This patient is a striking example of this problem.

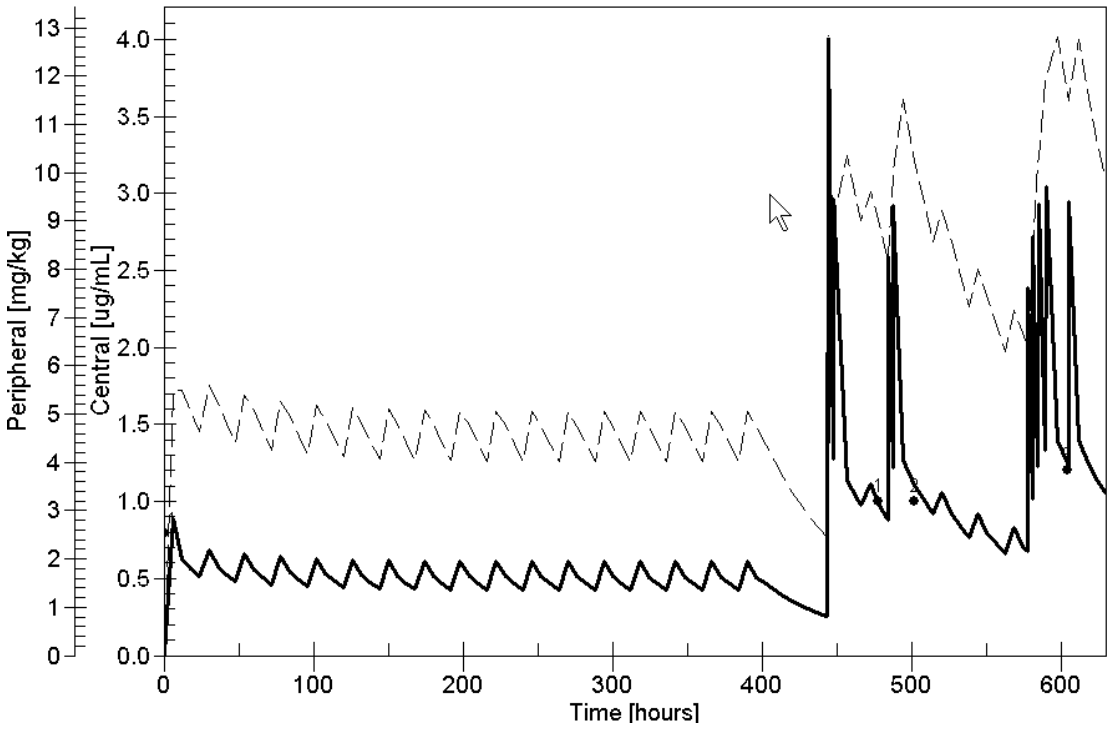


Figure 3. The three measured serum concentrations (dots) and their weighted average estimated values at the other times (the thick line), using the fitted 2 compartment digoxin model. At left, estimated concentrations (trough = 0.5 ng/ml) before onset of atrial fibrillation, Right of center, the dip in estimated concentrations from missing his dose that day, associated with the appearance of new onset atrial fibrillation. The three areas of higher serum concentrations reflect the three courses of extra intravenous digoxin that resulted in conversion to sinus rhythm three times, followed by recurrence of atrial fibrillation twice. The patient was in sinus rhythm for the third time at the right end of the plot, when a new dosage regimen, based on this analysis, was then developed for him.

The dashed line shows the weighted average estimated peripheral compartment values, using the 2 compartment digoxin model fitted to the serum concentration data. At left, estimated concentrations before onset of atrial fibrillation. Right of center, the dip in estimated concentrations from missing his dose that day, resulting in the appearance of new onset atrial fibrillation. The three areas of higher peripheral concentrations which reflect the three courses of extra intravenous digoxin that resulted in conversion to sinus rhythm, followed by recurrence of atrial fibrillation twice. The patient was in RSR when his peak peripheral concentrations ranged from 10 to 13 ug/kg. Vertical axis: serum concentrations in ng/ml, NOT ug/ml as shown, and peripheral compartment concentrations in ug/kg, NOT mg/kg as shown. Horizontal axis: hours into the regimen.

CLINICAL INTERPRETATION AND MANAGEMENT

Two important clinical questions are worth asking:

1. Was the patient in a true steady state each time before each serum sample was taken? The answer is clearly no. At the time of the first sample (1.0 ng/ml), he had just slipped back into AF. At the second, (also 1.0 ng/ml) he had just received extra digoxin doses and had just converted

back to RSR. The same for the third sample, which was 1.2 ng/ml. So he was not at all in the usual steady state to permit the conventional interpretation of the relationship between trough serum digoxin concentrations and clinical behavior.

2. Were the serum samples taken at the same time after the dose? No.
3. The clinical problem once again was what dosage regimen to consider using to maintain the patent in RSR. After his second conversion to RSR, he was again put back on the same regimen of 0.25 mg/day. After three days, the patient again reverted back to AF. At that time he had 7.0 ug/kg in his peripheral compartment. He was again titrated with five doses of 0.25 mg of IV digoxin over the next 36 hours. He again converted, for a third time, to RSR when he had 12.7 ug/kg in his peripheral compartment after analysis. A serum sample drawn 14 hours and 45 minutes after the fourth of those doses was 1.2 ng/ml, when he was in RSR. There was clearly no correlation between the raw data of the measured serum concentrations and the patient's clinical behavior. He was in AF with a concentration of 1.0, and in RSR with concentrations of 1.0 and 1.2 ng/ml. At this time the telephone consultation with us was done.
4. Such puzzling behavior is typical of that in many patients who are being monitored by measuring serum digoxin concentrations and looking for empirical clinical correlations with them. They simply are not there, and many internists and cardiologists are of the opinion that monitoring digoxin serum concentrations is not useful. They are quite correct, if one only looks at the raw data as presented above, and/or if one uses only a one-compartment pharmacokinetic model of digoxin which can only consider serum concentration data.
5. However, if one uses the above two compartment model based on the work of Reuning et el [4], and software to permit making an individualized patient pharmacokinetic model by using Bayes' theorem and fitting the patient's serum concentration data [19], one can see the plot of events in the peripheral compartment, as shown in Figure 3.
6. The relationship between the patient's clinical behavior and the profile of his measured and estimated serum concentrations was not at all clear (raw data = AF at 1.0, and RSR also at 1.0 and at 1.2 ng/ml), as in Figure 3). However, that between his clinical behavior and his computed peripheral concentrations was easy to see and understand immediately. For some reason, not clinically clear, the patient's requirements for digoxin had significantly changed, and he now only remained in RSR only when his computed peripheral compartment concentrations were between 10

and 13 ug/kg, not 5 ug/kg, as they had been before the patient missed his dose and developed AF.

7. Based on this analysis and on appraisal of his clinical behavior, a peripheral target peak goal of 11.5 ug/kg 7 hours after an oral dose was selected. An ideal dosage regimen of 468 ug, followed by 578 ug, and then by 572 ug/day was computed by the MM-USCPACK software. This was judgmentally revised to a first dose of 250 ug, and then (since 572 ug was about halfway between 500 and 625 ug), to 625 and 500 ug on alternate days. Clinical observation (see Figure 3) had shown that his previous maintenance dose of 250 ug/day was no longer able to maintain him in RSR, and that his estimated trough serum concentrations when he was previously in RSR were only about 0.5 ng/ml back then, and his estimated peripheral concentrations then were only about 5.0 ug/kg. On his new much larger dosage regimen, his estimated trough serum concentrations ranged from 0.88 ng/ml the first day to 0.92 after one week, and the target peripheral compartment goal of 11.5 ug/kg was predicted to be closely approximated. He was given the revised regimen above. The target goal was closely approximated, as shown in Figure 4. See [21] for a full discussion.

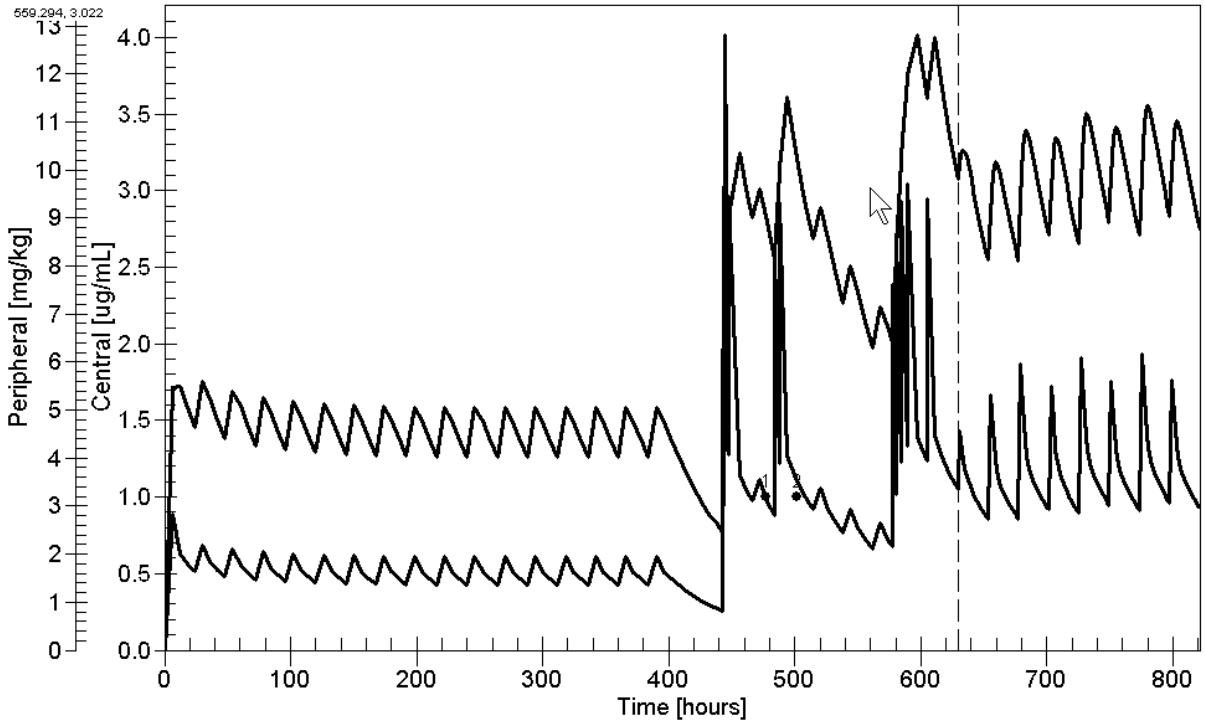


Figure 4. Plot of estimated serum and peripheral compartment digoxin concentrations (ug/kg) on planned future regimen (to the right of the vertical dashed line between past and future). Labels and axes as in Figure 2. Peak concentrations are close to the target of 11.5 ug/kg. Estimated trough serum concentrations are close to 1.1 ng/ml.

10. Now to the patient himself. On the above revised regimen, with events predicted as in Figure 4, he remained in RSR, and was able to leave the hospital in RSR, whereas a full week of therapy without such software assistance had been unsuccessful in maintaining the RSR which had been achieved on three separate occasions. Two weeks later, still on the above regimen, he was still in RSR when seen in the follow-up clinic. Unfortunately, no serum sample was obtained.

CONCLUSION

It is difficult to see so many thoughtful investigators strive for so little when they use only steady state trough serum data to make a population model, analyze it with a parametric method which does not have exact likelihoods, and then seek only to predict steady state serum concentrations of a drug, especially this important drug. So much more has been [4] and can be done. It is not difficult, using optimal experimental design and better methods for modeling and TDM, to do it.

Most encouraging clinical results have been obtained using a 2 compartment model and controlling the target peak peripheral compartment digoxin concentrations with regard to converting patients with atrial fibrillation and even chronic established atrial flutter to regular sinus rhythm. Patient behavior in the cases described here correlated well and immediately with the behavior of their individualized 2 compartment digoxin models. This is a new and provocative finding. It strongly suggests that digoxin can convert patients with atrial fibrillation, and even chronic established atrial flutter, to regular sinus rhythm, and maintain it for a considerable time. A 1 compartment model simply cannot show these important clinical relationships.

Modeling approaches and strategies for development of optimally individualized dosage regimens can result in significantly more capable clinical models and improved patient care. Much further work along these most interesting lines needs to be done.

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