Some Comments and Suggestions concerning Population Pharmacokinetic Modeling, especially of Digoxin, and its Relation to Clinical Therapy

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ABSTRACT

Population pharmacokinetic / dynamic (PK/PD) modeling is often employed to analyze data of steady state trough serum digoxin concentrations in the course of what is frequently regarded as routine therapeutic drug monitoring (TDM). Such a monitoring protocol is extremely uninformative. It permits only estimation of a single parameter of a one-compartment model, such as clearance. Use of D-optimal design strategies permit much more information to be obtained, employing models having really meaningful structure. Strategies and protocols for routine TDM policies greatly need to be improved, incorporating principles of optimal design.

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 will be in error, and the most likely results given the raw data will not be obtained. In addition, the likelihood as computed by NONMEM is only approximate, not exact. This impairs statistical consistency, and reduces statistical efficiency and the resulting precision of model parameter estimates. Other parametric methods are superior, as they provide exact likelihoods. However, they still suffer from the constraints of assuming the shape of the model parameter distributions.

Nonparametric (NP) methods are more flexible. One need not make any assumptions about the shape of the parameter distributions. NP methods also provide exact likelihoods, and 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 coefficient of variation. This is easy to do and permits more precise models to be made. This also permits estimation of assay error separately from the other sources of uncertainty in the clinical environment. This is most useful scientifically.

Digoxin has at least 2 compartment behavior. Its pharmacologic and clinical effects correlate not with serum digoxin concentrations, but with those in the peripheral nonserum compartment. Some illustrative clinical examples are discussed. Investigators have often used steady state trough concentrations only to make a 1 compartment model, and have sought only to predict future steady state trough
concentrations. Much more than this 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 frequently perform population studies of drug behavior in patients by using data of what they regard as routine therapeutic drug monitoring (TDM). This often involves analyzing data only of trough serum drug concentrations drawn in the steady state. In addition, the goal of such studies is often oriented only to predicting similar steady state trough concentrations in the future.

Provided are some comments and suggestions about this strategy, especially as it pertains to population modeling of digoxin, the use of serum digoxin concentrations in evaluating both the clinical as well as the pharmacokinetic and dynamic (PK/PD) behavior of the drug, and the utility of TDM combined with software employing nonparametric (NP) population models and multiple model (MM) dosage design for the optimization of digoxin therapy.

Investigators often use data of steady state trough serum digoxin concentrations to make 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 from other studies. 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.

The impression, held by many, is that one can make meaningful population PK models from such steady state, trough only, data. This is an illusion. Even though population models can obtain results from only a single sample per patient, no model having any real structure can be made from such minimally informative steady state trough only 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.

THE CRUCIAL ROLE OF INFORMATIVE DATA

An example of the crucial role of experimental design and the results obtained is shown in Figure 1, taken from 1. Figure 1A shows the results obtained using a nonparametric method of population analysis 2 to analyze data from a 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 only 20 measurements, one sample per patient, the highest peak obtained from ten of the patients, and the lowest trough from the other ten. Figure 1C shows the still more degraded results obtained by sampling only the single lowest trough from each patient. The figure reveals that the protocol used in obtaining data from which a population PK model is made has a truly profound effect upon the results obtained, even though the population modeling software actually works correctly, obtaining the most likely results given the data, in all cases.
Figure 1, A-C

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) joint parameter distribution. Results obtained from the full dataset of 177 measured gentamicin concentrations in 20 patients.

Figure 1B, center, shows the much different parameter estimates, based only on data of a single serum sample per patient, the highest peak in 10 randomly selected patients, and the lowest trough from the other 10 patients. Note the degraded results. Axes as in 1A.

Figure 1C, right, shows the even more different results when the dataset is restricted to only the single lowest trough sample from each of the 20 patients. Axes as in 1A.

A good discussion of the issues of optimal experimental design for guiding pharmacokinetic experiments, and of managing TDM in general is given by D’Argenio. Use of optimal design strategies can greatly increase the capability of any PK study and also of policies for routine TDM. They permit making either 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, it is suggested to draw serum samples at times close to the D-optimal times - a peak serum sample drawn either about 5 min after a 15 min intravenous (IV) infusion, for example, or about 1.5 to 1.75 hours after an oral dose, and a trough. In addition, it is often useful to supplement them with measurements taken 0.5 hour and 7 hours after a dose is given or started (by either route) to best estimate the rate constants from the central out to the peripheral compartment and back again. In managing digoxin patients using TDM, one can obtain not only a peak and trough pair in one dose interval, but also the other pair in a different dose interval, for example, going back and forth if needed.

One reason that monitoring trough serum drug concentrations has been so popular is that the effects upon the measurement obtained which are caused by errors in recording the times of dose administration and of drawing the blood are minimized when the trough sample is drawn. The result of that strategy, however, is that dynamic
information of drug kinetics over time is also minimized. Without kinetic information obtained by meaningful experimental design, as outlined by D’Argenio, no meaningful PK or PK/PD model can be made without better chosen data. This is another way of saying that it is always crucial to record accurately the times at which doses are given and serum samples are drawn. Also, in general, one probably needs to get, at a minimum, and over several dose intervals if needed, at least 1 sample for each model parameter to be estimated, either for a PK study or for a good routine TDM protocol.

Pharmaceutical companies may use D-optimal design to make population models, as they get better information from fewer patients at minimal cost. For example, they may begin by studying about 5 patients using an initial protocol, and then make a population model based on those 5 patients. Then they may calculate strategies to optimize the sampling protocol, and study 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. By using such an adaptively optimized sampling strategy they have obtained the most information from the fewest patients for the dollars spent doing the study.

SOFTWARE FOR POPULATION MODELING

NONMEM has probably been the most widely used population modeling software. It uses a parametric model. As such, it must assume the shape of the distribution of the model parameters, such as normal, lognormal, or perhaps bi- or multimodal. Some distributions, such as lognormal, may well be chosen for statistical convenience, avoiding negative parameter values in the distribution. The NONMEM estimates obtained are single point estimates of the model parameter means, variances, and covariances. These are estimates of mean and standard deviation, for example, of the single point parameter values in the equation which describes the assumed shape, such as that for a normal Gaussian distribution. That is why they are called parametric methods.

The word nonparametric, as used herein, specifically does not refer to noncompartmental models which are based on statistical moments, which have also been called nonparametric by some.

In contrast to parametric compartmental models and the above noncompartmental models, rigorous nonparametric (NP) population modeling methods estimate the entire model parameter distributions. There is no equation required anymore to describe any assumed shape of the model distributions. Further, if one uses a parametric model to develop a dosage regimen to achieve a desired therapeutic target goal, the separation principle states that the task is done suboptimally, as there is no performance index employed to evaluate and optimize the expected precision with which the selected therapeutic target goal will be achieved. Information from the full model parameter distributions is not available. One simply develops a regimen designed to achieve a desired target goal exactly, and knows that it will not do so.
In addition, the likelihoods computed by NONMEM are only approximate (the FO, FOCE, and similar algorithms). Because of this, results are approximate, with an error often approximately 2% for means, but approximately 30% for variances, and really gross, frequently in the opposite direction, for correlations. Because of those approximations, there is also no mathematical guarantee that if one studies more patients, the estimated parameter values will approach the true ones more closely. In short, there is no guarantee of statistical consistency. Other parametric methods, though, do have exact likelihoods, and do have the guarantee of statistical consistency. However, they still lack flexibility from assuming the shape of the assumed model parameter distributions, and from obtaining only single point estimates of those overall distributions. Even though the likelihoods obtained may be exact, if the assumed shape is not the correct (true) one given the data, the results will still be in error, as the likelihood obtained by such a constrained parametric method is often not the most likely one.

The parameter distributions provided by NP modeling methods obtain a discrete distribution, based on the theorems of Caratheodory, Lindsay, and Mallet. The NP model parameter distributions thus consist of multiple discrete points (support points), up to 1 per patient studied in the population. In addition, the likelihoods calculated are exact, and statistical consistency is assured. Each discrete support point (see Figure 1) consists of an estimated value for each model parameter, and an estimate of the probability of that point in the population. In such discrete population distributions, subpopulations such as fast and slow metabolizers are easily recognized without further effort.

There has recently been a nonparametric option implemented in NONMEM. It appears to be superior to the parametric methods in NONMEM. However, for determining the location of the support points, that 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 errors in locating the support points, as shown by Leary et al. Because of this, the simplified nonparametric method in NONMEM is demonstrably inferior to the rigorous methods discussed above.

MULTIPLE MODEL DOSAGE DESIGN

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, the future predictions obtained from each support point are weighted by its estimated probability. It is then easy to calculate the weighted squared error with which any dosage regimen fails to hit a specific desired therapeutic target goal at the desired time. This optimization process continues iteratively 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. MM design and MM
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 the process of Bayesian forecasting. It requires real control, not simply forecasting. The MM-USCPACK software \(^{19}\) uses NP population modeling (now the Pmetrics software) and MM dosage design (now the RightDose software) to obtain maximally precise dosage regimens. It also uses MM Bayesian adaptive control. It is the combination of NP modeling and MM RightDose software that permits maximally precise MM Bayesian adaptive control, rather than the less capable parametric population modeling and maximum a posteriori probability (MAP) Bayesian adaptive control. MM Bayesian adaptive control develops dosage regimens, individualized for each patient, which achieve 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 goal in either the central (serum) or, especially, in the peripheral (nonserum) compartment.

Instead of merely using a population modeling method with which to do a study, simply because it is available, investigators should 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 scientific reasons why they have selected a particular population modeling method for use in their studies.

**ANALYSIS OF ASSAY ERRORS AND THEIR USE IN FITTING DATA**

Weighting schemes used in fitting models to data have 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 that overall error is due to the assay error and how much is due to all other factors in the clinical environment, 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 any changing parameter values during the period of data analysis. The real quantitative information of the assay error itself is all too often discarded once it is regarded as being acceptably precise.

Instead of using the assay percent coefficient of variation (CV%), as has usually been done to reflect assay precision and credibility, one can first determine the standard deviation (SD) of the assay itself, expressed not as the percent coefficient of variation (CV%) but as the actual SD itself of each particular assay measurement. One must first get the SD of the assay anyway in order to calculate the CV%. If one obtains the assay SD, one can square that to get the variance of the measurement at each measured concentration. Then one can give weight to the assay concentration using the reciprocal of the assay variance at that point, to obtain the Fisher information of each data point \(^{20,21}\). The method of determining the assay error as a polynomial function of replicate
concentrations measured over the working range of the assay is described in 21. Further, if one does this, then one does not need to censor low measured concentrations perceived as having an unacceptably high CV% 21, which are commonly regarded as being below the limit of quantification. There are many assays such as those for HIV, HCV, and HBV, for which, in addition to drug concentrations, there is no scientific reason to censor any low values at all. Instead, with appropriate treatment, one really wishes to drive those measurements to zero, fully down 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 replicate measurements of several samples ranging from the blank to extremely high values, as described in 21. The remaining error due to the environmental factors can then easily be estimated separately and distinctly from the previously determined assay error polynomial, as also described in 21.

For example, one can estimate gamma, in the MM-USCPACK and its new Pmetrics population modeling software 22. Gamma is a multiplicative environmental error term. If gamma is 2.0, it means that the total noise, assay plus environmental noise, is twice the assay error. If so, one can be comforted, as the environmental error is relatively 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. A defect of gamma is that it multiplies the assay error polynomial, further accentuating its polynomial curvature.

If desired, one can now choose instead to estimate an additive term which we call lambda, instead of the multiplicative term gamma. Estimating lambda is probably a better strategy than estimating gamma, as it does not multiply up the usual curvatures present in the assay error polynomial 21. It examines lambda as an SD, as well as the SD of each measured concentration. It squares each SD to get their variances, adds them to get the total variance, and then takes the square root of that to reflect the overall SD present at that measurement time. In this way, the two error variances are more equitably added to reflect the total uncertainty present at the time each measurement was made, giving a better reflection of the relative combination of how the two errors, assay and environmental noises, act together to make the overall population model.

MODELING DIGOXIN.

A common clinical study of digoxin PK has been to use a 1-compartment model. However, Reuning et al 4 and others 23-27, 37 have clearly shown 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. These important works generally appear not to have been appreciated.

The USC Laboratory of Applied Pharmacokinetics created an adult population model based upon the work of Reuning et al. In this model, there is an absorptive
compartment into which oral doses are given, a central compartment into which IV infusions are given and from which serum concentrations are measured, and a peripheral nonserum compartment which reflects overall tissue concentrations. Since only serum concentrations can be measured, only the central (serum) compartment has a definite apparent volume of distribution. In contrast, concentrations in the peripheral compartment can never be observed. Only amounts of drug in that compartment can be calculated. In our model, these amounts are normalized by dividing them by the patient’s estimated concentrations in the peripheral compartment, as ug of drug per kg body weight).

We estimated the concentrations resulting from standard dosage regimens in patients regarded as being average, as well as the resulting D-optimal times to obtain blood samples. We developed software to calculate dosage regimens of digoxin to achieve selected target concentration goals at selected target times, in either the serum or in the peripheral compartment. For target trough serum concentrations of about 0.9-1.0 ng/ml, conventional dosage regimens of about 250 ug/day largely achieve these goals in average patients when renal function is normal, and one can see that the peak peripheral compartment concentrations are about 7 ug/kg. This model has worked extremely well clinically in our hands for individualizing digoxin dosage regimens in patients of differing body weight and renal function who have regular sinus rhythm.

**DIGOXIN SERUM CONCENTRATIONS**

The range of serum digoxin concentrations generally regarded as being therapeutic is often said to be 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 clear that quite a few patients tolerate serum digoxin concentrations well over 3 ng/ml, and actually as high as 6.5 ng/ml, without any toxicity. In addition, patients with atrial fibrillation (AF) who have good atrioventricular nodal conduction often require serum concentrations of about 2.0 ng/ml for adequate control of ventricular rate. Others have commented on the inadequacy of therapeutic serum concentrations to get good rate control in AF. However, it seems not to have been considered by most cardiologists that patients with AF might require their own separate therapeutic ranges or target concentrations.

Rigid use of current therapeutic ranges also neglects the great variation in sensitivity of individual patients to digoxin, or to any drug. Doherty has also shown that patients may tolerate quite high serum digoxin concentrations, up to 6.5 ng/ml without toxicity. For example, I have seen a patient with AF who required a serum concentration of 8.0 ng/ml for adequate ventricular rate control, (without toxicity), and a colleague has had a patient who required 6.0 ng/ml to obtain the same effect. This great variation in sensitivity, possibly due to genetic polymorphism in determining the binding constants of digoxin to membrane Na – K ATPase, seems to have been overlooked by many clinicians, who are taught to live in awe of guidelines such as therapeutic ranges. Such ranges are usually never explicitly defined, except by eye, and
are usually developed by committees who have never seen the particular patient under one’s clinical care. Clinicians should accept their individual clinical responsibility rather than evade it by blindly following such guidelines. Instead, they should look carefully at each individual patient’s clinical response, and consider and select a specific serum compartment, or especially, a peripheral compartment target digoxin concentration which appears best for each particular patient, based on his/her need for the drug. It is most likely that the concentration of digoxin in the serum itself 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, the toxic effects.

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 appears to result in the increased inotropic effect of digoxin. In addition, almost all the manifestations of digitalis toxicity are also seen in patients with hypercalcemia from any cause – the anorexia, nausea, vomiting, arrhythmias, delirium, and psychoses. The visual symptoms seen with digoxin toxicity 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 apparently 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 afterimages in the retina, thus causing the many and varied visual symptoms.

**DIGOXIN IN ATRIAL FIBRILLATION**

In addition to treating patients with regular sinus rhythm (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 to decide upon the proper dosage regimen to maintain the peripheral concentration found when conversion has been obtained. This clinical decision after obtaining successful conversion is what is all too often impossible to reach without guidance by PK/PD models and software.

One might perhaps consider carefully titrating a patient up to a target serum trough digoxin concentration of about 1.5 – 2.3 ng/ml for control of ventricular rate, and to perhaps a peak peripheral concentration of 9-13 ug/kg, and sometimes up to 18 ug/kg of body weight, at 7 hours after an oral dose, or 4 hours after an IV dose, for conversion to RSR. Watch the rate, watch for toxicity, and watch for conversion to RSR. Note that it is well described 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, is widely cited as having shown this. The problem is that the study was...
extremely underpowered. There were only 18 patients each in both the study arm and in the control arm, making it almost impossible to detect any significant difference between them. Further, they gave digoxin only in the form of a fixed protocol, rather than by using thoughtful clinical titration, and did not report the age, weight, or renal function of their patients. Eight of 18 placebo patients spontaneously converted within 24 hours, compared with 9 of 18 in the digoxin arm. It is quite possible that Falk et al did not give enough digoxin to obtain the desired effect, as discussed below. If one assumes a fairly average 65 year old man, 70 inches tall, weighing 70 kg, with a serum creatinine of 1.0 mg/dL, his estimated creatinine clearance is 69mL/min/1.73 m².

If one uses the RightDose software and the oral digoxin protocol described by Falk et al which was to give 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 resulting predicted trajectory of the weighted average estimated serum concentrations over the first 24 hours. The highest predicted serum concentration is 1.8 ng/ml, and the final concentration is 1.4 ng/ml, 10 hours after the last dose above.
Figure 2 also shows the time course of the estimated digoxin concentrations in the peripheral nonserum compartment, based on the model of Reuning et al. The highest concentration was 8.0 ug/kg, only a little higher than the 7.0 ug/kg associated with reasonable therapy for patients in congestive failure with RSR, and with a predicted steady state trough serum concentration of 0.9 – 1.0 ng/ml 24 hours after the last dose.

Another interesting study was that of the DAAF Trial Group in which 239 patients with new onset AF were given intravenous digoxin. Their average age was 66.2 years, and weight was 78.2 kg. Half were male and half female. They received intravenous digoxin (duration of infusion not stated) at average doses of 0.455 mg, 0.308 mg, and 0.318 mg at 0, 2 and 6 hours into the regimen respectively. If one assumes that their average serum creatinine was 1.0 mg/dL, and gives the above regimen intravenously, the simulated results using the RightDose software showed a peak serum concentration of 3.91 ng/ml at the end of the infusion of the 2nd dose and 3.90 at the end of the 3rd dose. The predicted weighted average peak concentration in the peripheral compartment was 9.23 ug/kg at 9.25 hours into the regimen. The estimated 95% distance ranged from 7.9 to 11.0 ug/kg. This is slightly but not significantly higher than that predicted from the study of Falk above. The DAAF group found a significant relationship between the concentration of digoxin in their peripheral compartment with regard to slowing of ventricular rate in patients with AF, but was not able to find such a relationship with regard to conversion to RSR. Again it is likely in retrospect that they did not give enough drug.

Another study by Jordaens et al examined still higher doses in 19 patients randomized to IV digoxin and 20 to placebo. Average body weight was 73 kg. They gave 0.75 mg at the start, over 10 min, then 0.25 mg over 5 min at 4 hours, and another 0.25 mg over 5 min at 8 hours into the regimen. Nine digoxin and 8 placebo patients converted to RSR. Digoxin also slowed the ventricular rate significantly. If one gives the regimen they received to a simulated patient of their stated average age, and weight, and assumes a height of 70 in, male gender, and serum creatinine of 1.0 mg.dL, the peak predicted serum concentrations using the population model in the RightDose software were 6.9 ng/ml at the end of the first infusion, with 95 percentile estimates from 5.15 to 7.82 ng/ml. The next highest peak was 3.89 ng/ml at 8.0 hours into the regimen, with 95 percentile estimates ranging from 2.6 to 5.3 ng.ml. Peak concentrations in the peripheral compartment were 11.25 ug/kg at 11.55 hours into the regimen, with 95 percentile estimated distances ranging from 9.5 to 12.9 ug/kg. In this study, they clearly gave more drug, and had higher estimated concentrations in the peripheral compartment, using the RightDose software.

Calculated peripheral compartment digoxin concentrations in those patients at the time of conversion ranged from a low of 9.5 to a high of 18 ug/kg. In these three studies, individualized clinical titration for each patient was not done, nor was renal function evaluated.

Weiner et al examined the clinical course of patients with acute AF treated with rapid IV digitalization. Renal function was evaluated but not stated. Body weight and the duration of IV infusion of digoxin were not stated. An initial dose of 0.5 mg was given,
then another 0.5 mg IV at 4 hours, then 0.25 mg at 8 hours, and finally 0.25 mg at 12 hours. In that nonrandomized, non placebo-controlled observational study, 40 of 47 episodes of AF in 45 patients were converted to RSR. Assuming a 65 year old man, 70 kg, 70 in tall, with a serum creatinine of 1.0 mg/dL (creatinine clearance of 69 ml/min/1.73 M²), predicted weighted average peak serum concentrations of 5.49 ng/ml were reached at 4.2 hours into the regimen, with 95 percentile distances from 4.1 to 7.7 ng/ml, at the end of the second IV infusion. The next peak was 4.33 ng/ml at 12.2 hours (the end of the last infusion). Percentile distances were 2.9 to 6.0 ng/ml. Weighted average predicted concentrations in the peripheral compartment peaked at 13.9 ug/ml at 15.32 hours into the regimen, with 95 percentile distances from 11.6 to 16.0 ug/kg.

In my own experience with 3 out of 4 patients with AF that I have been involved with, conversion to sinus rhythm was achieved by careful incremental clinical titration with digoxin, either oral or IV, observing the patient for rate control, toxicity, or for conversion to RSR. In the fourth, who was also hyperthyroid, the rate was well controlled, without toxicity. One of the patients who converted was on digitoxin, and had had chronic stable atrial flutter with 2/1 atrioventricular block for the past three years.

An illustrative clinical example was discussed in Jelliffe et al. 21, a patient with new onset atrial fibrillation who 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 a successful maintenance dosage regimen was developed. Finding the correct maintenance dose without such models is a real problem clinically because the relationships between doses, serum and peripheral compartment concentrations, and clinical response cannot be seen or evaluated quantitatively. Models and software are required.

Figure 3 analyzes the data of the patient previously described in Jelliffe et al. 21. It represents a telephone consultation with William Nicholson, M.D., when he was a cardiology fellow at Stanford. The patient was a 58 year old man, 68 in tall, weighing 75 kg, with a stable serum creatinine of 0.8 mg/dL. He had been in a steady state in regular sinus rhythm (RSR) on chronic oral digoxin maintenance therapy of 0.25 mg/day. However, the patient 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.

The next clinical question was what dosage regimen to give next to keep him in the RSR that had once 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 really changed or not. However, he excreted his extra digoxin, and went back into AF within two days of such maintenance therapy. At this point a serum digoxin sample was 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 second of the above two doses, when he was in RSR. The concentration, surprisingly, was exactly the same – 1.0 ng/ml.

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 ug/L) 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 regions 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 of center, 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 regions of higher peripheral concentrations 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. Labels and axes as in Figure 2.

The important clinical question is - how can someone be in AF at one time and in RSR at another time and have exactly the same serum concentration? It is strongly felt by many cardiologists that serum digoxin concentrations do not correlate at all well with clinical behavior. The patient described here is a striking example of this.

CLINICAL INTERPRETATION AND MANAGEMENT
Two related questions are worth asking. First, 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 the 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. Second, were the serum samples taken at the same time after the dose? Again, no.

The clinical problem once again was what dosage regimen to decide upon in order to maintain the patient 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. At that time he had 12.7 ug/kg in his peripheral compartment after the pharmacokinetic analysis. There was no clinical evidence of toxicity. A serum sample drawn 14 hours 45 minutes after the fourth of those doses was 1.2 ng/ml, and 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. It was at this time that the telephone consultation with us was done.

Such puzzling clinical behavior is typical of that seen in many patients who are being monitored by measuring occasional serum digoxin concentrations and looking for empirical clinical correlations with them. They simply are not there, and many internists and cardiologists strongly feel that monitoring digoxin serum concentrations is simply not useful. They are quite correct, if one only looks at the raw data as presented above, and/or if one uses only a 1-compartment pharmacokinetic model of digoxin which can only consider serum concentration data.

However, if one uses that raw data and analyzes it with the above 2-compartment model based on the work of Reuning et al ⁴, and uses software to permit making an individualized patient pharmacokinetic model by using Bayes’ theorem and fitting the model to the patient’s serum concentration data ¹⁹, one can see the plot of that patient’s events in the peripheral compartment, as shown in Figure 3.

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 at 1.0 and at 1.2 ng/ml), as in Figure 3. However, the relationship between his clinical behavior and the profile of his computed peripheral compartment concentrations was immediately easy to see and understand. For some reason, not clinically clear, the patient’s requirements for digoxin really had changed, and he now remained in RSR only when his computed peripheral compartment concentrations ranged between 10 and 13 ug/kg, not down to about 5 ug/kg, as they had been before the patient missed his dose and developed AF, as shown in Figures 3 and 4.
Figure 4. Plot of estimated serum and peripheral compartment digoxin concentrations (ug/kg) on the 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 ug/L.

Based on this analysis, coupled with appraisal of the patient’s clinical behavior, a target peak goal in the peripheral compartment of 11.5 ug/kg 7 hours (the usual peak time 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 RightDose 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, which averages 562.5 ug/day. Clinical observation (along with Figure 3) had shown that his previous maintenance dose of 250 ug/day was no longer able to maintain him in RSR, that his estimated trough serum concentrations back when he was previously in RSR were only about 0.5 ng/ml, and that his estimated peak peripheral concentrations back then were only about 5.0 ug/kg. He may well have been underdigitalized back then, with reduced bioavailability of oral digoxin. On his new 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 described above. The target goal was closely approximated, as shown in Figure 4. See 21 for a full discussion.

On the above revised regimen, with events predicted as in Figure 4, the patient 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 already been achieved before on two separate occasions before, but not successfully maintained. 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.

Hornestam et al have also modeled digoxin as a 2 compartment model with an effect compartment. In their placebo-controlled study of patients with AF, they were not able to find a relationship to conversion to RSR, but did find an effect with respect to the reduction of ventricular rate. That response was proportional to the baseline ventricular rate at start of therapy, and was linearly related to the computed digoxin concentration at the effect site, similar to the relationship between computed concentration in the peripheral compartment and inotropic effect found by Reuning et al. It thus appears that both contractility and slowing of ventricular rate in patients with AF appear linearly related to computed digoxin concentrations in a peripheral nonserum location.

**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 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 target peak peripheral compartment digoxin concentrations with regard to converting patients with atrial fibrillation 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 does convert some patients with atrial fibrillation, and even with chronic established atrial flutter, to regular sinus rhythm, and maintain it. A 1-compartment model simply cannot show these important clinical PK/PD relationships, and cannot lead to the same informed clinical dosage decisions.

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

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**References:**


