Digoxin and Digitoxin Convert Atrial Fibrillation and Flutter to Regular Sinus Rhythm with Pharmacokinetically Optimized Dosage Regimens.

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Abstract

**Background** - Does digitalis convert atrial fibrillation or flutter (AF) to regular sinus rhythm (RSR)? In several studies digoxin was no better than placebo. Therapeutic serum digoxin concentrations are 0.5 to 2.0 ng/ml. However, sensitivity to digoxin varies widely, rate control in AF is often not achieved until 2 ng/ml, and many patients tolerate much higher concentrations.

**Methods** - Pharmacokinetic (PK) models of digitoxin and digoxin containing a peripheral nonserum effect compartment, based the work of Reuning et al., were developed. Effect correlates with peripheral compartment, not serum, concentrations.

**Results** - Most patients with RSR do well at serum digoxin concentrations about 1.0 ng/ml and peripheral concentrations about 7.0 ug/kg. Three of four patients with AF were converted using classical clinical titration with incremental doses, plus therapeutic drug monitoring and guidance from the models. Those who converted did so when peripheral concentrations of 9 to 18 ug/kg were reached. No toxicity was seen. Successful maintenance was achieved by dosage regimens to maintain peripheral concentrations present on conversion. The fourth patient did not convert, and reached peripheral concentrations of only 6-7 ug/kg.

**Discussion** – Literature search shows that attempts at conversion were unsuccessful with regimens achieving less than 9 ug/kg in the peripheral compartment. However, one study that converted 40 of 47 patients achieved peripheral concentrations of 14 ug/kg.

**Conclusion** – Conversion to RSR does not occur until higher peripheral concentrations than usual are reached. These findings correlate well with those of others. Further work is needed to evaluate these provocative findings.

**Key words:** digoxin, digitoxin, atrial fibrillation, atrial flutter, individualized drug dosage, pharmacokinetics, population pharmacokinetic models, multiple model dosage design.

List of Abbreviations:

AF = Atrial Fibrillation or Flutter
CCr = Creatinine Clearance
PK = Pharmacokinetic
PD = Pharmacodynamic
RSR = Regular Sinus Rhythm
Introduction

Treating and stabilizing patients with atrial fibrillation or flutter (AF) with digoxin has always been somewhat elusive. While control of ventricular rate is often achieved by titrating the patient with incremental doses of digoxin, it has been controversial whether or not digoxin is able successfully to convert patients with AF to RSR and to maintain them there, and the general impression I have heard has been that it is not at all useful in converting patients with atrial flutter, especially chronic, well-established atrial flutter, to RSR.

The therapeutic range of serum digoxin concentrations is often taken to range from about 0.5 to 2.0 ng/ml. Most patients with digoxin toxicity have serum concentrations above 2.0 ng/ml, and most clinicians have been loath to accept serum concentrations any higher. The therapeutic range of serum digitoxin concentrations is from about 10 to 35 ng/ml.

However, there is great variation in sensitivity to digitalis glycosides. Doherty showed that while most toxic patients have serum digoxin concentrations above 2.0 ng/ml, there are many who tolerate quite high levels, and that in his series, as many patients with serum concentrations of 3.0 ng/ml and above tolerated those concentrations as were toxic. I have seen a patient who had required 500 ug of digoxin by mouth 3 times daily in order to control his ventricular rate with his AF. He did not have a problem with oral absorption. His serum digoxin concentration was 8.0 ng/ml. He had then been switched over to digitoxin, and then required 400 ug of digitoxin daily for maintenance, with a serum digitoxin concentration of 115 ng/ml. I have had a colleague in Albuquerque who had a similar patient with AF who required a serum digoxin concentration of 6.0 ng/ml for adequate rate control. It is highly likely that these unusual patients may have had genetically determined differences in the binding constants of digitoxin and digoxin to their Na-K ATPase.

Population pharmacokinetic models of digitoxin and digoxin, composed of an absorptive compartment for oral dosage, a central serum concentration compartment, and a peripheral, nonserum compartment which is correlated with the pharmacological effect of the drug, based on the model of Reuning et al., were made. Using these models, two of three patients with atrial fibrillation and one with chronic stable atrial flutter were successfully converted to regular sinus rhythm (RSR) and maintained thereafter. The literature was reviewed, and various therapeutic scenarios were examined using these models.

The clinical impression of lack of correlation of the patient’s clinical response with serum digoxin concentrations was confirmed with these models. However, clinical effect correlates more closely with the profile of computed digitalis concentrations in the peripheral tissue compartment than with serum concentrations. The literature was reviewed. Studies showing failure of digoxin to convert AF to RSR compared to placebo had lower computed peripheral compartment concentrations, using our models, than did those in studies of patients who were successfully converted. The studies associated with successful conversion by digoxin achieved higher peripheral
compartment concentrations, in the same general range as those associated with successful conversion in the three patients described herein. Based on these case reports and the review of the literature, digitalis does appear to convert patients with AF and one with chronic stable atrial flutter to sinus rhythm. Successful maintenance of RSR requires correct dosage to maintain the tissue concentrations associated with successful conversion. Success requires guidance using pharmacokinetic software and the pharmacokinetic models employed here for both conversion and proper maintenance.

The Population Pharmacokinetic Model of Digitoxin

The population model of digitoxin was made in 1978 as part of a study of the bioavailability of digitoxin, supported by Lilly Laboratories. The bioavailability and pharmacokinetic behavior of digitoxin, given intravenously, intramuscularly, in oral solution, and in three tablet forms, to 22 healthy volunteers was studied. Bioavailability was evaluated by comparison of areas under the serum concentration curve and also by computation of the initial condition in the absorptive compartment at time zero. The overall bioavailability of oral digitoxin tablets was found to be 75%.

While the general relationship of the percent of digitoxin eliminated by metabolism is about 75%, with about 25% excreted renally, this can lead to a problem when the model is fitted to serum concentration data in an essentially anuric patient. Such a patient may have an elimination rate constant less than that the average found in anuric patients, due to the significant variability in the behavior of the drug between patients. This would result in a bad fit to the data and an erroneous model for the patient. Because of that, the estimated percent of drug eliminated by metabolism was here was judgmentally reduced by 20% from 75% to only 55%, yielding a rate constant for metabolic metabolism of 0.018875 hr\(^{-1}\). Because of this, renal elimination was assumed to be 45%, with a rate constant of 0.000151 per unit of creatinine clearance (CCr), resulting in a rate constant for renal excretion of 0.0151 hr\(^{-1}\) when CCr is 100 ml/min/1.73 M\(^2\). This results in a safer model in which it is highly unlikely that a patient will be found who would have an overall elimination rate constant less than that of the metabolic rate constant shown here. As a result, the relationship between renal function and excretion will almost always be positive, greater than zero.

Using this model to develop a loading and maintenance digitoxin dosage regimen designed to achieve and maintain a clinically selected target trough serum concentration goal of 15 ng/ml for a 65 year old man, 70 in tall, 70 kg body weight, with a serum creatinine of 1.0 mg/dL results in an idealized total loading dose of 750.88 ug, followed by 104.6 ug daily thereafter. This is easily and practically approximated by a 750 ug total loading dose, with 100 ug/day thereafter. The estimated peak serum concentration is 22 ng/ml with the first dose, and 18 ng/ml thereafter. All predicted trough serum concentrations are 15.0 ng/ml, as desired. Estimated peak concentrations in the peripheral compartment are 6.2 ug/kg, with trough concentrations of 5.4 ug/kg. The loading dose should be divided into 2 or 3 parts every 6 hours, checking for toxicity before giving the next part.
We can see that when we develop such a regimen to achieve a trough serum concentration of 15 ng/ml, we are also achieving peak concentrations in the peripheral compartment of 6.2 ug/kg and troughs of 5.4 ug/kg once a steady state has been reached. Adjusting dosage to body weight and renal function to achieve such individualized clinically selected specific target goals for each patient is essential.

The Population Pharmacokinetic Model of Digoxin

The population model of digoxin has been described previously ⁴. It was also based on the work of Reuning et al ⁵. However, to make it more applicable for maximally precise clinical use with newer maximally precise techniques of multiple model dosage design ¹²-¹³, its model parameter values (means and standard deviations - SD's) were converted into discrete model parameter distributions with a computer program developed for this purpose, using the method of maximum entropy ¹⁴. In this way, the entire parameter distributions (not just single point estimates of mean values) permit development of maximally precise digoxin dosage regimens, individualized to an adult patient’s age, gender, body weight and renal function, to achieve clinically selected specific target goals in either the central (serum) or peripheral (effect) compartment, using the method of multiple model (MM) dosage design ¹²-¹³. In addition, much of the above problem seen with anuric patients with digitoxin is avoided here because all digoxin model parameters are the entire distributions, and not just single point parameter estimates ⁴,¹⁴.

We can see that in the process of developing a dosage regimen to achieve and maintain a commonly desired target trough serum digoxin concentration of 0.9 ng/ml, we are actually developing a regimen to achieve and maintain a target peak concentration in the peripheral compartment of about 6.8 ug of digoxin per kg of body weight. Thus common target trough serum concentrations of 0.9 ng/ml are achieved when we develop regimens to achieve peaks of 6.8 ug/kg in the peripheral compartment, once a steady state has been reached (about 8 days with normal renal function, about 3 weeks in essentially anephric patients). These relationships are shown in Figure 3.

Comparing these two models, we can also see that with the above quite conventional dosage regimens of digitoxin and digoxin for typical patients, approximately equal peripheral compartment concentrations are achieved with both drugs. This suggests that the concentrations achieved with these drugs are approximately equally effective and therefore probably have similar potency. The findings with these models are similar to those found with earlier more simple one compartment models in which approximately equal total body stores of these drugs also had approximately equal potency ¹⁵,¹⁶.

Implications for dosing in acute clinical situations – Managing Atrial Fibrillation and Flutter.

In addition to approaches to patients with RSR who are stable and who need only a regimen to achieve and maintain a stable target serum concentration, other
patients, especially those with atrial fibrillation or flutter (AF), require judicious titration with incremental doses to control ventricular rate or to convert them to RSR. This can be done, judiciously, but patients with AF usually require larger doses, and the serum concentrations do not reflect a patient’s rapidly changing clinical behavior. The commonly accepted therapeutic range of serum digoxin concentrations is from about 0.5 to 2.0 ng/ml. However, patients with AF who have good atrioventricular conduction require serum concentrations of about 2.0 ng/ml. Others have described the inadequacy of serum concentrations in the therapeutic range to control ventricular rate adequately in patients with atrial fibrillation. It thus appears that patients with AF require a higher general target therapeutic range of serum digoxin concentrations, probably somewhere from 1.5 to perhaps 2.4 ng/ml. A good part of the problem is that when one wishes to control patients in such acute clinical situations, since their clinical behavior at a particular time does not correlate with measured serum concentrations, many clinicians have come to believe that serum level monitoring is not useful. When one only looks at the raw data of the measured serum concentrations, they are quite right. However, as shown by these models, it is really the concentrations in the peripheral effect compartment that correlate with clinical response, especially in rapidly changing situations, rather than the serum concentrations themselves. Nevertheless, the measured serum concentrations, coupled with the use of models of this type, are the only way to calculate and evaluate the complex and otherwise incomprehensible relationships between the doses given, the serum concentrations, and the resulting concentrations in the peripheral effect compartment, in order to correlate everything with the patient’s overall clinical response, and to develop the dosage regimens then required to achieve and maintain desired target concentrations clinically chosen for each individual patient according to his/her perceived need for the drug, in either the serum or the effect compartment. This point is made especially clear by the behavior of the patient described in Case 3 further on. Peripheral compartment peak target goals of 6 to 8 ug/kg appear appropriate for most patients with congestive failure and RSR, while higher target peak goals (9 to 18 ug/kg) are often needed to achieve good rate control or conversion in patients with AF.

For patients with AF, after one has titrated the patient with incremental doses and achieved a desired clinical goal such as good rate control or conversion to RSR, the really difficult problem has then been to plan the clinical next move - to develop the correct maintenance dosage regimen that keeps the patient in the clinical state one has successfully achieved. Without guidance by models and software such as those described herein, this is usually impossible. Four illustrative case reports are now presented.

**Case 1 – A Patient with Chronic Stable Atrial Flutter**

This patient represented the author’s first experience with serial titration, monitoring serum concentrations, and using these pharmacokinetic models for dosage guidance. RL was a 65 year old man, 69 in tall, weighing 75 kg. His serum creatinine was stable at 1.0 mg/dL. He had had several small transient ischemic attacks and was
admitted for physical therapy and rehabilitation. He had been in chronic atrial flutter for about three years, with 2/1 AV block, and a ventricular rate of 140/min. He was well anticoagulated on coumadin both in the past and throughout his entire hospital course. He had been maintained on oral digoxin 0.25 mg three times a day for much of those three years. He had had several attempts in the past to “push” his digoxin dosage, but without success. His serum digoxin concentration on presentation was only about 1.5 ng.ml, which is low for his quite high dose, suggesting a bioavailability problem.

It was first thought that he might have organisms in his intestine which might be metabolizing his digoxin to inactive dihydro forms. He was placed on tetracycline for a week, with no response clinically. Because of that, digoxin was stopped, and he was placed on digitoxin, as it is actually the safer drug. Digoxin has been thought to be safer because its half time is shorter and is more rapidly excreted. However, shorter half time drugs require more frequent observation for equal safety. Just as a patient progresses rapidly from an initial state of having a short duration drug in his body to that of not having it any more, going from the initial to the final state in approximately five short drug half-times, so also does such a patient progress more rapidly into toxicity as renal function decreases without dosage adjustment, for example. Digitoxin is longer acting and therefore more clinically stable than digoxin from day to day, and is less sensitive to changes in renal function. It also has better bioavailability and therefore more reproducible bioavailability from day to day. Especially because of its longer half-time and therefore slower response to day to day variations in dosage and renal function, toxicity can be detected in earlier stages of its slower onset than with digoxin. In addition, because it is somewhat more lipid soluble, the first manifestation of digitalis toxicity is perhaps somewhat less likely to be a life-threatening arrhythmia and somewhat more likely to be anorexia, nausea, vomiting, or some other manifestation of central nervous system toxicity. Further, for any stated frequency at which a patient is seen, toxicity will be detected in an earlier stage of its development with a longer acting drug such as digitoxin, when it is less likely to constitute a threat to life.

The patient was therefore begun on digitoxin, 0.2 mg/day. His clinical response and his serum concentrations were frequently monitored with peak (1.5 hr after a dose) and trough levels, and also samples at 0.5 and 7 hours after a dose. Throughout this period of deliberately slow progressive clinical titration, rate control was the only clinical goal. There was no thought of converting him to RSR. Titration consisted of increasing the peripheral compartment target goal by 25 or 30% about 2 or 3 times a week, monitoring his serum digitoxin concentrations, analyzing his data, and computing the dosage regimen to achieve the new goal. After the first 12 days, he developed occasional 3/1 AV block, but no significant slowing of his overall ventricular rate.

The titration continued. In the next 4 days, he developed occasional 4/1 AV block, but still no really significant slowing of his ventricular rate. The target concentration in his peripheral compartment was progressively increased, giving the required doses. These became rather large, just as he had been on large doses of digoxin before, documenting his poor oral absorption of both drugs. However, his serum concentrations also were becoming elevated above 25 ng/ml, the toxic cutoff used by
the laboratory. Setting his target goal and developing the required dosage to achieve it, though, was always guided by his clinical behavior. There was no evidence of toxicity at any time. His serum concentrations were by now about 40 ng/ml peak and 25 ng/ml trough. His ventricular rate was about 125/minute. The surprise came at 19 days, when he suddenly converted to regular sinus rhythm at 110/minute. His peripheral compartment concentrations at that time were 17 ug/kg.

Now the question was - what dose to put him on to keep him in his sinus rhythm? The required dosage was about 0.7 mg/day to keep that target peak goal in his peripheral compartment. The other surprise was that this conversion did not seem to be a fluke – his RSR persisted. His serum concentrations ranged from about 50 ng/ml peak to about 40 ng/ml trough.

Everything continued stable until day 25, when he developed an aspiration pneumonia. His chest x-ray showed infiltrates, and his arterial oxygen saturation was low. Everything went back to before – atrial flutter, 2/1 AV block, and a ventricular rate of 140/minute again. A slightly higher target goal was set and the necessary doses were given. The major factor here was that at day 28, his pneumonia was better and his arterial oxygen saturation improved. When that happened, he once again returned to RSR. After that, all dosage was kept as it was. He remained in RSR but had two more episodes of aspiration pneumonia, with return to flutter each time, showing the effect of his hypoxia against the effect of digitoxin. Digitoxin dosage was kept constant throughout these other two episodes. After each episode of aspiration was treated and his oxygen saturation improved again, he returned to regular sinus rhythm each time. RSR persisted until he sadly died after a total of about 6 weeks. More than three of those weeks were spent in RSR. No evidence of digitalis toxicity or any other arrhythmias were seen at any time. Plots of his measured serum concentrations and his estimated central and peripheral concentrations are shown in Figure 1 A + B.

Without this software, this pharmacokinetic model, and its ability to provide the overall structure to see and understand the quantitative relationships between his doses, serum concentrations, peripheral concentrations, and his clinical behavior, it would have been impossible to develop the correct dosage regimen for him, and to recognize how much of the problem was poor bioavailability, how much was due to the kinetics of the drug, how much drug was in the peripheral nonserum compartment, and exactly how all this related to his overall clinical behavior and the effect of his hypoxia with his episodes of aspiration pneumonia. No evidence of digitalis toxicity was seen at any time. In contrast to the pharmacokinetic behavior of digoxin, the correlation of the behavior of this patient on digitoxin was much better with respect to his measured serum concentrations than that of digoxin, due to the greater stability and longer half time of digitoxin. This is also easily seen by comparing Figure 1 with Figures 2-4 further on.
Case 2 – An elderly lady with new onset AF and end stage renal disease.

AC was a 92 year old lady who was coming to the end of her life because of an inoperable transitional cell carcinoma of the bladder which had obstructed her ureters and produced severe renal failure, with a serum creatinine of 8.0 mg/dL. She had stopped taking food or medicines by mouth. She was preparing to die. One day she became acutely dyspneic, with acute pulmonary edema, wet rales halfway up both her posterior lung fields, and new onset rapid AF with a ventricular rate of 170/minute. She was 66 in tall and weighed 75.75 kg. Her estimated creatinine clearance \( \text{CCr} \) was only 3.9 ml/min/1.73 M\(^2\).

She was given oxygen, diuretics, and an initial dose of 500 ug of digoxin intravenously over 5 minutes. After 3 hrs 20 min, her ventricular rate had fallen to 135/min, she felt a bit better, and a dose of 250 ug was similarly given intravenously. Shortly after, however, she developed atrial flutter with 2/1 AV block, and her ventricular rate actually increased to 150/min. This was a clinical puzzle, as it raised the question of digoxin toxicity. Because of this, she was watched and monitored very closely. After 7 hours, she reverted back to atrial fibrillation, but with larger fibrillatory waves on her EKG than before, as is commonly seen in such titrations of patients with AF on digitalis glycosides. It therefore seemed clinically likely that she might have developed her flutter as larger portions of her atrial myocardium were participating in the less random pathways of atrial depolarization, and that this was still evident now, with her larger fibrillatory waves. It thus seemed that slightly more digoxin might further facilitate this process. If so, it might bring about RSR if the entire atrial myocardium should participate in depolarization again. Because of this, and because she was again in fibrillation with a still inadequately controlled ventricular rate, she was given one more dose of 250 ug intravenously. After one hour and 15 minutes, she converted to RSR at 110/min.

Now the clinical question was what dosage regimen to place her on to keep her in the sinus rhythm which had been achieved. Using the RightDose software \(^{24}\) and the population model of digoxin described here, her data, doses, and her extremely low CCr were entered into the program. As shown in Figure 2 A and B, the profile of her predicted serum concentrations was not helpful in understanding what was going on. However, the profile of her estimated peripheral concentrations correlated very well with the evolution of her clinical status. Her ventricular rate dropped as the peripheral compartment concentrations gradually rose with the doses of titration, and she converted to sinus rhythm when her weighted average estimated peripheral concentration was about 9.3 ug/kg. A slightly higher target peripheral concentration of 9.5 ug/kg was clinically selected for her, and the regimen was developed to achieve and maintain that peak target goal. The ideal intravenous regimen was 141 ug/day. The ideal weekly maintenance dose was then 141 times 7 = 987 ug/week. This ideal was approximated by a practical weekly dose of 1000 ug/week, or 8 doses of 125 ug intravenously per week, each infused over 15 minutes. Based on this, a daily dose of 125 ug was given for 3 days, then a single dose of 250 ug the next day, followed by 125 ug daily for the remainder of the week, and so on. On this regimen, designed to
maintain the peripheral compartment concentration near the desired target goal of 9.5 ug/kg, the patient remained in RSR for the next two weeks of her life, until she died of a pneumonia. Titrating her ventricular rate and following her clinical response showed that she converted to RSR when her peripheral compartment concentration was about 9.3 ug/kg. Her subsequent regimen was designed to maintain her peripheral compartment concentration in this general range. It was successful in maintaining her in RSR until her final demise. No evidence of digitalis toxicity was present at any time. In this particular lady, no serum concentrations were measured. A plot of her entire clinical course is shown in Figure 2 A and B.

Case 3 – A patient already converted three times.

Figure 3 below summarizes the analysis of this patient, previously described by Jelliffe 9,23. 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 RSR on chronic oral digoxin maintenance therapy of 0.25 mg/day. However, he missed a dose one day and developed new onset rapid AF. He was titrated with 4 IV doses of 0.25 mg each, given over 1 day, and at that time he converted to RSR.

His previous maintenance dose of 0.25 mg/day was again resumed. However, he went back into AF within two days, as that maintenance regimen did not maintain the peripheral compartment concentration at the value associated with his successful conversion, as shown in Figure 3. 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. He was again titrated with extra IV digoxin and 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.

Three Questions

The first 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? Many cardiologists feel that serum digoxin concentrations do not correlate at all well with clinical behavior, and that monitoring serum concentrations is not useful because of that. The patient described here is a striking example of this.

Second, was the patient in a true steady state each time before each serum sample was taken? The answer is clearly no. At 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 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 serum digoxin concentrations and clinical behavior. Third, were the serum samples taken at the same time after the dose? Again, no.
After his second conversion to RSR, he had again been put back on 0.25 mg/day. After three days, he again reverted back to AF. At that time he had only 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. There was no 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 thus no visible correlation between the raw data of the measured serum concentrations and his 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. His renal function was quite good. His estimated CCr was 98 ml/min/1.73 M².

Such apparently puzzling clinical behavior is seen in many patients who are being monitored by measuring occasional serum digoxin concentrations, looking for empirical clinical correlations with such raw data. 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 looks only at the raw data. However, when one fits the model to the patient’s serum concentration data, one can see the plot of that patient’s events in both central and peripheral compartments, as shown in Figure 3 A and B.

The clinical problem once again was what dosage regimen to give to maintain him in RSR. In contrast to his serum compartment data, the relationship between his clinical behavior and the profile of his computed peripheral compartment concentrations was easy to 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 5 ug/kg, as they had been before the patient missed his dose and developed AF, as shown in Figure 3 A and B.

Based on this analysis, and correlating it with the patient’s clinical behavior, a target peak goal in the peripheral compartment of 11.5 ug/kg at 7 hours (the usual peak time after an oral dose) was clinically selected for him. 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, or an average of 562.5 ug/day. His previous maintenance dose of 250 ug/day was no longer able to maintain him in RSR. With the information provided by his fitted model, as in Figure 3, one can see that his estimated trough serum concentrations back when he had previously been in RSR were only about 0.5 ng/ml, and his estimated peak peripheral concentrations back then had only been about 5.0 ug/kg. On his new dosage regimen described above, 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 individualized, clinically selected, target peripheral compartment goal was closely approximated, as shown in Figure 3B.

On that regimen, with events predicted as in Figure 3 A and B, he remained in RSR, and was then able to leave the hospital in RSR, whereas the previous full week of therapy had been unsuccessful. 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 then.

**Case 4 – A very large, heavy patient.**

DD, a 41 year old man, 71 in tall, weighing 300 pounds, was in chronic AF. His serum creatinine began at 0.6 mg/dL, rose to a high of 1.4 mg/dL, and then fell again to 0.8 mg/dL. His estimated creatinine clearance thus began with a high value of 205 ml/min/1.73 M². It then fell to 75, and then rose again to 155 ml/min.1.73M². His ventricular rate was about 130/min throughout, with little change during his therapy.

His initial dosage began at 250 ug/day, but rapidly rose to 500 and 875 ug/day in divided doses, checking the patient before each next dose, and finally to a high of 1250 ug/day for one day, followed by 1000 ug/day. All this was carefully done, checking the patient before each dose of 250 ug in the various increments to achieve the total daily doses described above. At this point others involved in his care did not wish to keep up these high doses, even though 1000 ug/day for a 300 lb man is equivalent to 500 ug/day for a 150 lb person.

During this time he had a total of 10 serum concentrations measured. They ranged from a low of 0.9 to a peak of 2.7 ng/ml. When his data was fitted the RightDose software, a hybrid Bayesian fitting procedure was used which can reach out beyond the stated ranges of the parameter values of the population model, which was developed from patients not so heavy. In this way, a good fit was obtained to his serum concentration data, as shown in Figure 4 A. In this data-rich analysis, his peripheral compartment concentrations reached a high of only about 6 ug/kg, as shown in Figure 4 B. This very heavy patient’s behavior thus correlated well with that of other patients whose clinical response with regard to conversion to RSR was not significantly different from placebo.

**Review of the Literature.**

Digoxin is often said to be no better than placebo for converting patients with atrial fibrillation to sinus rhythm. The study by Falk et al is widely cited concerning this. That study was extremely underpowered. There were only 18 patients each in both the study arm and control arm, making it almost impossible to detect any significant difference between them. Further, they gave digoxin only as a fixed protocol, rather than by classical clinical titration. They also 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 65 year old man, 70 inches tall, weighing 70 kg, with a serum creatinine of 1.0 mg/dL, his estimated creatinine clearance is \(69\text{mL/min/1.73 m}^2\). If one uses the RightDose software and gives the above simulated patient the oral digoxin protocol described by Falk et al which was 0.6 mg orally at first, 0.4 mg at 4 hours, 0.2 mg at 8 hours, and finally 0.2 mg at 14 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.

More importantly, the average estimated peripheral concentration reached was only 8.0 ug/kg, as shown in Figure 5. This is just slightly more 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.

The DAAF Trial Group studied 239 patients with new onset AF who were given intravenous digoxin. The study was a randomized, double blinded, multicenter trial of digoxin versus placebo. 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 mean doses of 0.455 mg, 0.308 mg, and 0.318 mg at 0, 2 and 6 hours into the regimen respectively. Fifty six of 122 placebo patients (46%) converted to RSR, and 60 of 117 patients (51%) in the digoxin group. If one assumes that their average serum creatinine was 1.0 mg/dl, and gives the above regimen intravenously, the results using the RightDose software showed a predicted 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 peripheral peak concentration reached 9.23 ug/kg at 9.25 hours into the regimen, as shown in Figure 5. This is only slightly higher than that predicted for the study of Falk above. They found a significant slowing of ventricular rate in the patients with AF, but no significant correlation with conversion to RSR. Again it is likely in retrospect that they did not give enough drug, only reaching an average peripheral concentration of 9.23 ug/kg.

The DAAF data was also used to make a population pharmacokinetic model of digoxin. The authors of the modeling study found that a 2 compartment model with central and peripheral compartment fit the data better than a 1 compartment one, and also showed that the reduction in ventricular rate correlated well with computed concentrations in their peripheral compartment.

Jordaens et al examined still higher doses in another underpowered study of 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 peripheral concentrations were 11.25 ug/kg at 11.55 hours into the
regimen. They gave more drug, and had somewhat higher estimated concentrations in the peripheral compartment, using the RightDose software, as shown in Figure 5.

In none of those three studies was individualized clinical titration for each patient done, nor was renal function evaluated. While they often found a significant reduction in ventricular rate, none of these authors found a significant difference from placebo with regard to conversion to RSR.

In contrast, Hou et al.\textsuperscript{10} compared IV digoxin with amiodarone in 50 patients randomly assigned to digoxin or amiodarone for conversion of AF to RSR. Digoxin was given as an average total dose of 910 ug/70 kg in three divided doses IV over 30 minutes every 2 hours. Average age was 70 years, weight was normalized to 70 kg, renal function and height were not stated. Assuming 70 in height and serum creatinine = 1.0 mg/dL, the digoxin population model predicts an average measured serum concentration of 1.25 ng/ml at 24 hours after the start of the digoxin, with an estimated peak peripheral concentration of 8.8 ug/kg. When the model was fitted to the average serum concentration they found, 1.02 ng/ml, the estimated peak peripheral concentration was 9.0 ug/kg, due to a slightly different profile over time. They found that digoxin achieved conversion to RSR in 17 of 24 patients (71%), as shown in Figure 5.

Similarly, Weiner et al.\textsuperscript{11} studied 47 episodes of AF in 45 patients treated with rapid IV digitalization. Renal function was evaluated but not stated. Body weight and infusion duration were not stated. They gave an initial dose of 0.5 mg, another 0.5 mg IV at 4 hours, 0.25 mg at 8 hours, and 0.25 mg at 12 hours, for a total of 1.5 mg. In that nonrandomized, non placebo-controlled observational study, 40 of 47 episodes of AF in 45 patients were converted to RSR. Assuming our 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 M\(^2\)), the average predicted peripheral concentrations peaked at 13.9 ug/ml at 15.32 hours into the regimen, as shown in Figure 5. The increased peripheral compartment concentrations they achieved correlated well with their results compared to those of the other studies, and with those achieved in the three cases reported herein who converted to RSR. It thus appears that both contractility and slowing of ventricular rate in patients with AF, and also now, conversion to RSR, appear to be essentially linearly related to computed digoxin concentrations in a peripheral nonserum location, as does conversion to RSR.

Three other studies\textsuperscript{27-29} examined the ability of digoxin, often in combination with quinidine, to convert AF to RSR. While the protocols are reasonably described, the specifics of the dosage regimens of digoxin were not described precisely enough to permit rigorous pharmacokinetic analysis.

Discussion

Selection of the target digoxin goal is something that must be carefully individualized by the clinician for each patient. Guidelines set down by committees, such
as a therapeutic range of serum digoxin concentrations from 0.5 to 2.0 ng/ml, are generally useful for many patients, but clearly not for all. No committee has seen any particular patient who is cared for by any individual physician. No committee can dictate what course of action carries the best expected value for an individual patient they have not seen. All it can do is to recognize general trends. Because of this, it becomes each individual physician’s responsibility to consider carefully just how much any particular patient needs the drug, how dangerous the patient’s individual situation is without it, and how great a risk of toxicity the clinician feels is acceptable in order to obtain the effect of the drug that is hoped for. If the patient does not need the drug very much, only a low risk of toxicity is acceptable. One selects a low target goal and gives a gentle regimen to achieve it. On the other hand, if the patient shows that he/she is in significant danger and needs the drug “pushed”, one then selects a higher target goal and develops the more aggressive dosage regimen to achieve it. Doing this with maximal precision, using multiple model dosage design 12,13, allows this to be done with maximum safety as well. Even in patients with congestive failure and RSR, Hoeschen and Cuddy showed that one can often improve the benefit of many conventional dosage regimens by carefully selecting a higher target goal and giving a somewhat higher dosage regimen to achieve it. Such approaches have been shown to result in improved myocardial function 30. Their average serum concentration in patients receiving maintenance dosage of 0.25 mg/day was 0.56 ng/ml, while on 0.5 mg/day it was 1.2ng/ml. In their hands the optimal dosage was 0.43 mg/day. In their study, they showed a significant inverse correlation between left ventricular ejection time and the serum digoxin concentration. Their findings indicate that patients who clinically appear not to be receiving full or adequate effect from their digoxin dosage may well benefit from careful dosage escalation, guided, for example, by modeling, dosage design, and serum level monitoring.

The old saying that “the right dose of digitalis is enough” has never been more true. In today’s world of serum concentrations and fear of using one’s individual judgment, using guidelines to avoid guilt rather than accepting one’s real responsibility as a thoughtful advocate for each patient’s individually optimized therapy, digoxin is too often thought of as a last-line drug. It is not used nearly enough. Pharmacokinetically designed approaches to drug therapy badly need to be taught to medical students in a clinically meaningful way, and most physicians are not trained in the techniques of drug therapy that can be achieved with pharmacokinetic approaches such as those described herein.

Lastly, digitalis toxicity is considered as something that is diagnosed by its clinical manifestations. Serum concentrations are often used to aid in the recognition of digitalis toxicity. In fact, in diagnosing digitalis toxicity, there is actually nothing to diagnose. The patient’s clinical behavior, whether nausea, vomiting, an arrhythmia, or a psychosis, has a well known list of causes, such as a high serum digoxin concentration, hypoxia, hypokalemia, hypercalcemia, or hypomagnesemia, and of course, heart disease, for example. One can easily simply go through such the list of well known causes of such behavior and optimize them as much as possible. The cell responds to the total environment which surrounds it. The patient in Case 1 is a good illustration of the
combined factors in the intra and extra cellular environment and the development of arrhythmias, for example.

Conclusion

Based on the cases reported here, and on the review of the literature, digitalis glycosides convert patients with atrial fibrillation, and even chronic, well-established atrial flutter, to RSR, and maintain them there. The key is the use of pharmacokinetic models which describe the behavior of these drugs, and which, coupled with thoughtful measurement of serum concentrations, permit more informed approaches to dosing. Essential to this approach is the need to compare each individual patient’s clinical behavior with his/her pharmacokinetic model, setting each patient’s individualized target goal based on that comparison, and development of the required dosage regimen to achieve it. Pharmacokinetic models, Bayesian adaptive control, and pharmacokinetic approaches to dosing provide the structure for this approach. Further work appears indicated to evaluate these interesting and provocative findings, and perhaps to re-examine the role digoxin may be able to play in the pharmacological approach to patients with AF, not only in the context of obtaining good rate control, but also in going that extra bit to convert them to RSR and maintain them there.

References

3. Jelliffe R: The Bioavailability and Pharmacokinetic Behavior of Digitoxin. Technical Report 2012-1, Laboratory of Applied Pharmacokinetics, University of Southern California School of Medicine, Los Angeles, CA.


Figures

Figure 1A
Figure 1B

Figure 1A: Case 1, the first 32 days

Figure 1 A+B: Left vertical axis – Serum digitoxin, ng/ml. Left vertical axis – serum digitoxin, ng/ml. Right vertical axis – Peripheral compartment concentration, ug/kg body weight. Horizontal Axis – time into regimen. Upper line, estimated peripheral compartment digitoxin concentration. Lower line, estimated serum digitoxin concentration. Crosses, measured serum digitoxin concentrations.
Figure 2. Profile of estimated serum digoxin concentrations (2A) and peripheral concentrations (2B) in Case 2. Horizontal Axis – Hours into regimen. Vertical Axis – Central compartment (serum) concentrations (2A), not in ug/ml as stated in the plot, but in ng/ml. In 2B, vertical axis - peripheral compartment concentrations, not in mg/kg as stated, but in ug/kg. Vertical bars at bottom: times of doses. Patient converted to RSR after dose 3, and remained in RSR for the remainder of her hospital course, about 1 week after the end of the plots.
Figure 3, A and B – Plots of Central (3A) and Peripheral (3B) compartment concentrations in patient Case 3. Axes as in Figure 2. The patient missed his usual daily dose of 250 ug of digoxin at 400 hours, and went into fast AF. He converted at RSR at 450 hrs, went back into AF at 475 hrs, back into RSR at 490 hrs, back into AF at 570 hrs, and back into RSR at 600 hrs. The target peak goal of 11.5 ug/kg was closely approximated by the regimen given thereafter, and he remained in RSR thereafter. Note the clarity of the relationship between his clinical behavior and the peripheral compartment concentrations, and the lack of such clarity between his behavior and his central (serum) concentrations.
Figure 4 A and B

Figure 4A

Figure 4B

Figure 4 A and B – Plot of central and peripheral concentrations in Case 4. Axes as in Figure 2. Note the failure of this patient to convert at peripheral concentrations of 6 ug/kg.
Figure 5. Plot of percent conversion achieved in cases 1, 2, 3, and 4 (triangles) and in studies by Jordaens et al (J), the DAAF group (D), Falk et al (F), Hou et al (H), and Weiner et al (W). P indicates the placebo response found in the D, J, and F studies. Each P is connected to its respective digoxin result with a line.