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A Two – Compartment Population Pharmacokinetic- Pharmacodynamic Model of Digoxin in Adults, with Implications for Dosage

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Abstract

A population pharmacokinetic/pharmacodynamic (PK/PD) model of digoxin in adult subjects was originally developed by Reuning et al in 1973. They clearly described the two - compartment behavior of digoxin, the lack of correlation of effect with serum concentrations, and the close correlation of the observed inotropic effect of digoxin with the calculated amount of drug present in the peripheral, nonserum, compartment.

Their model seemed most attractive for clinical use. However, to make it more applicable for maximally precise dosage, its model parameter values (means and standard deviations (SD's) were converted into discrete model parameter distributions using a computer program developed especially for this purpose, using the method of maximum entropy. In this way, the parameter distributions became discrete rather than continuous, suitable for use in developing maximally precise digoxin dosage regimens, individualized to an adult patient's age, gender, body weight and renal function, to achieve desired specific target goals in either the central (serum) compartment or in the peripheral (effect) compartment, using the method of multiple model (MM) dosage design. Some illustrative clinical applications of this model are presented and discussed. This model with a peripheral compartment reflecting clinical effect has contributed significantly to an improved understanding of the clinical behavior of digoxin in patients than is possible with models having only a single compartment, and to the improved management of digoxin therapy, for over 20 years.

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Disclosures

The authors declare no conflicts of interest.

Keywords

Digoxin; Population Modeling; Pharmacokinetics; Pharmacodynamics; Digoxin Therapy; Maximum Entropy

Introduction

This population model with a peripheral, nonserum compartment described here has been most useful in planning, monitoring, and adjusting individualized digoxin dosage regimens not only for relatively stable patients in congestive heart failure with regular sinus rhythm, but also for managing acute clinical situations in patients with atrial fibrillation or flutter, in which clinical events move too rapidly for the events to be reflected in the serum concentrations, but where they are easily described by the good correlations with concentrations in the peripheral effect compartment. This population model is now an integral part of the Bestdose computer software for developing maximally precise individualized drug dosage regimens for patients [1].

Methods

The original population model

The present model was made in a quite unusual way. Originally, a 2 compartment model of digoxin in adult subjects was described by Reuning et al [2]. That model consisted of a central (serum concentration) compartment which received intravenous doses, and from which samples for measuring serum digoxin concentrations could be taken. There was also a peripheral pharmacodynamic compartment. Computed concentrations in that effect compartment were shown to have an essentially linear relationship to the inotropic effect of digoxin, as described by changes in indices of myocardial contractility [2].

For the central serum compartment, the serum concentration is described as the amount of drug in that compartment at a stated time divided by the apparent volume of distribution of that compartment.

In contrast, the peripheral (effect) compartment is not observable, as it is a mathematical abstraction. It represents all the rest of the absorbed drug in the body that is not present in the serum compartment. Because concentrations in that compartment cannot be directly observed, no volume of distribution can be estimated for it. To normalize this compartment, its computed total amount of digoxin, which is easily calculated from the serum concentration data, is divided by the patient's body weight and is expressed as ug of drug per kg of total body weight. In addition, an absorptive compartment for oral dosage was added to their initial model. Oral bioavailability was assumed to be 65%.

The overall model is parameterized as V_c (L/kg), the apparent volume of distribution of the central (serum) compartment; K_{nr} (hr^{-1}), the nonrenal component of the rate constant for elimination; K_r , its renal component, in units of hr^{-1} per unit of creatinine clearance ($\text{ml}/\text{min}/1.73\text{m}^2$ body surface area); K_{cp} (hr^{-1}), the rate constant from the central out to the peripheral (effect) compartment; K_{pc} (hr^{-1}), the rate constant back from the peripheral to

the central compartment, and K_a (hr^{-1}), the rate constant for absorption of an oral dose from the gut.

The value of V_c was taken as the mean of the three studies of patients with normal renal function described by Reuning et al [2], Table 1, p 129, which equaled 110 L. Adjusting this for an assumed average 70 kg man gave a value of 1.5714 L/kg. The overall elimination rate constant for subjects with normal renal function was 0.0747 hr^{-1} . Assuming that digoxin is approximately 61 % eliminated by renal excretion and 39 % by nonrenal metabolism, the renal rate constant becomes 0.0451 hr^{-1} . Assuming that the renal rate constant occurs at a creatinine clearance (CCr) of 100 ml/min/1.73 m^2 , that overall renal rate constant translates into a value K_r of 0.000451 hr^{-1} for each unit of CCr. The 39 % nonrenal rate constant of elimination K_{nr} thus becomes 0.0288 hr^{-1} . The K_{cp} was taken from the mean value of 0.56 hr^{-1} for patients with normal renal function, and the K_{pc} was similarly taken as 0.15 hr^{-1} . The variability in the parameter distributions was assumed to be 20 %. Thus the standard deviations (SD's) around the mean parameter values were 0.314 L/kg for V_c , 0.0001 hr^{-1} for K_r , 0.112 hr^{-1} for K_{cp} , 0.03 hr^{-1} for K_{pc} , 0.1219 hr^{-1} for K_a , and 0.0058 hr^{-1} for K_{nr} . In this report, creatinine clearance has been estimated as described previously [3].

Conversion of the Original Continuous Model Parameter Distributions to Discrete ones

The original model of Reuning et al was converted into a nonparametric format [4] having multiple discrete parameter distributions most suitable for clinical use, employing maximally precise multiple model (MM) dosage design [5–7]. This was done by a computer program developed in our laboratory specifically for this purpose [8]. In this program, the parameter means and SD's were entered along with their ranges, and the desired number of support points for each model parameter. The discrete distribution was computed in which the location and probability of each discrete model parameter support point was estimated, using the method of maximum entropy. In this way, the least informed discrete distribution most closely matching the entered parameter means and SD's was obtained [8].

Results

We obtained 64 discrete support points for this model. Table 1 shows the discrete parameter distributions obtained for the maximum entropy population digoxin model. They consist of 64 discrete support points having the values shown in Table 1. Each of the 64 rows in Table 1 describes a discrete support point. Each support point contains an estimated value for each model parameter (the columns), and in the left column, the estimated probability of that support point in the population. The probabilities sum to 1.0. Table 2 shows the statistical summaries of the model parameter distributions. each at the 4 corners of the population ranges, each with its own probability, as shown in Table 1.

Discussion

The model described here describes the behavior of digoxin in adult patients, and the relationship between serum concentrations and concentrations in the peripheral effect compartment. It thus provides a structure for planning, monitoring, and adjusting dosage regimens of digoxin for patients, based on their body weight and their renal function, to

achieve desired target goals in either the serum or in the peripheral effect compartment in a maximally precise manner, using the method of multiple model dosage design [5–7].

Implications for Dosage - Achieving Target Trough Serum Concentration Goals

Using this model, if one assumes a 65 year old man, 70 in tall, weighing 70 kg, with a serum creatinine of 1.0 mg/dL, his estimated CCr [3] is 69.14 ml/min/1.73 M². If one wishes to develop an initial oral loading and daily maintenance digoxin dosage regimen to achieve and maintain a desired trough serum concentration of 0.9 ng/ml (a common clinical target goal for someone in congestive heart failure with regular sinus rhythm), the ideal suggested dosage regimen to achieve that target goal is a total loading dose of 1027 ug, given in 3 parts 6 hours apart, checking for effect and toxicity before giving each next part, followed by 261 ug for the 2nd day, tapering gradually down (due to the 2 compartment behavior of the drug) to 251 ug for the eighth day.

The ideal dosage regimen suggested above can easily be approximated by a more practical one of a total loading dose of 1.0 mg, given as 500 ug initially, followed by 250 ug at 6 hours, and by another 250 ug at 12 hours, checking for toxicity before giving the next part, then followed by 250 ug daily for maintenance thereafter.

Figure 1 shows the estimated weighted average serum concentrations resulting from this revised ideal regimen. The peak serum concentration occurs about 1.5 to 1.75 hours after an oral dose, or at the end of an intravenous infusion. After the first of the daily maintenance doses, starting on the 2nd day, the predicted weighted average peak serum concentration is 1.2 ng/ml, ranging from 0.7 to 1.8 ng/ml. At the eighth day the predicted peak weighted average serum concentration is 1.3 ng/ml. The variation in the peak serum concentration at that time ranges from about 0.8 to 1.7 ng/ml. On this quite practical and conventional dosage regimen, all the weighted average predicted trough serum concentrations for that week are quite close to the desired target value of 0.9 ng/ml, ranging from 0.7 to 0.9 ng/ml.

Figure 2 shows the estimated peripheral compartment concentrations over the same 8 days of initial therapy. Note that the concentrations in the peripheral effect compartment do not correlate with serum concentrations, as they rise when the serum concentrations are falling sharply due to distribution from central to peripheral compartment.

The predicted weighted average peak concentration in the peripheral compartment occurs about 7 hours after the dose. The weighted average prediction after the first maintenance dose on day 2 is 6.8 ug/kg, and ranges from 4.9 to 8.0 ug/kg. This time course of the predicted peripheral compartment concentrations in this figure parallels the inotropic effect of the drug as shown by Reuning et al [2]. After that, the peaks gradually rise over a week to a weighted average of 7.5 ug/kg on the 8th day, and range from about 3.8 to 10.5 ug/kg. The predicted trough concentrations average 5.8 ug/kg, and range from about 2.8 to 9.5 ug/kg at that time.

However, the weighted average peak peripheral concentrations of about 7.1 ug of drug per kg of body weight, which are reached about 7 hours after each oral dose, do correlate quite

well with trough serum concentrations of 0.9 ng/ml at 24 hours after each dose, once a steady state has been reached.

We can see that in the process of developing a dosage regimen to achieve and maintain a target trough serum 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 7.0 ug of digoxin per kg of body weight. Thus common target trough serum concentrations of 0.9 to 1.0 ng/ml are achieved when we develop once daily dosage regimens to achieve peaks of 6.8 – 7.3 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).

Individualizing Dosage to Body Weight and Renal Function

Patients with greater body weight require proportionally greater doses, and smaller patients will need smaller doses. Similarly, those with reduced renal function will also require smaller maintenance doses. For example, the model suggests that for the same target serum concentration goal for a patient similar to the above patient, but having severely compromised renal function with a serum creatinine of 5.0 mg/dL and a creatinine clearance of 12 ml/min/1.73 m² [3] will probably require an ideal loading dose of 864 ug (again, divided into 3 parts, each 6 hours apart) followed by 138 ug on the 2nd day, tapering down to 132 ug on the 8th day. In this case, because of the reduced maintenance dose, the weighted average peak serum concentration falls to 1.2 ng/ml, in order to result in 0.9 ng/ml at the trough. Because of this, somewhat lower peak concentrations are achieved in the peripheral compartment, only an average of about 6.0 ug/kg, ranging on day 8 from 3.5 to 8.4 ug/kg.

A practical approximation of this ideal regimen can be represented by a total loading dose of 875 ug (seven tablets of 125 ug each) given, for example, as four, two, and one tablet at time zero, six, and twelve hours into the regimen (again, checking for toxicity before giving each next increment), followed by 125 ug daily thereafter. The results of this modified regimen are shown in Figures 3 and 4. On the 8th day of therapy, peak serum concentrations average 1.4 ng/ml, ranging from 0.8 to 1.8 ng/ml., with trough concentrations averaging 0.9 ng/ml, and ranging from about 0.6 to 1.3 ng/ml. Similarly, on the eighth day, predicted peak peripheral compartment concentrations average 5.8 ug/kg, and range from 3.4 to 8.3 ug/kg, while the trough peripheral concentrations average 5.3 ug/kg, and range from 3.0 to 7.9 ug/kg.

Individualized Dosage for Younger Patients with better Renal Function

Renal function is generally better in younger patients, and they need higher maintenance doses. For example, let us consider a similar patient, but who now is only 20 years old. If his serum creatinine is again 1.0 mg/dL, his estimated creatinine clearance is now 108 ml/min/1.73 m² body surface area. The suggested ideal regimen to hit a target trough serum concentration of 0.9 ng/ml is a total loading dose of 1149ug, in three parts 6 hours apart, followed by 351 ug on day 2, tapering down to 341 ug by the eighth day. All predicted trough weighted average serum concentrations are 0.9 ng/ml. They range from 0.5 to 1.4 ng/ml. Similarly, predicted concentrations in the peripheral compartment on day eight are a

weighted average peak of 7.1 ug/kg, ranging from 4.1 to 11.8 ug/kg, and troughs of 5.9 ug/kg, ranging from 3.0 to 10.4 ug/kg.

The above ideal regimen can be readily approximated by a more practical one of 1125 ug for the total loading dose (9 tablets of 125 ug, given as 500, 375, and 250 ug, 6 hours apart, checking for toxicity before giving each next part), followed by an ideal average daily maintenance dose of 345 ug/day. Here, the total weekly maintenance dose is 345 times 7 = 2415 ug/week. Dividing 2415ug by 125ug yields 19.32 tablets of 125 ug each. This is easily approximated practically by 19 tablets of 125 ug given over each week. This approach shows the utility of calculating the total weekly maintenance dose rather than just the average daily maintenance dose. With 2 such tablets per day accounting for 14 of the 19 tablets, then the other doses of 250 ug can be given 5 days per week, for a total of 2375 ug/week. Thus one can give the patient a regimen of 375 ug/day for 5 days per week, and 250 ug for 2 days per week. One should space the 2 days of no extra dosage as widely apart as possible over the week, for example, on Sundays and Wednesdays. The patient can easily write this regimen down on a calendar to refer to each day for the correct dosage. The results of this practical revision of the ideal regimen are shown in Figures 5 and 6. Peak predicted peak serum concentrations average 1.6 ng/ml, and range from 1.2 to 2.5 ng/ml after 8 days. Peak peripheral concentrations average 7.0 ug/kg after 8 days, and range from 4.1 to 11.9 ug/kg at that time, while trough predictions average 6.1 ug/kg, and range from 3.0 to 10.3 ug/kg. The variation in all the predictions seen with this population model underscore the need for therapeutic drug monitoring and further dosage individualization for each patient.

The combination of multiple model dosage design [5–7] to give the most precise regimen to hit a specific desired target goal (selected for each patient based on the physician's individualized clinical consideration of the need of each individual patient for the drug and the risk of toxicity felt to be acceptable for that patient's need), coupled with calculating the total weekly maintenance dose, results in a combination of precision and practicality that has not been previously achieved with other approaches to digoxin dosing [9].

Variability in Response: The need for monitoring serum concentrations and dosage adjustment

The figures presented here illustrate the utility of this model in planning initial dosage regimens of digoxin for individual patients, adjusted to their body weight and renal function. They also illustrate (especially in Figures 5 and 6) the significant variability in the predicted responses of patients from whom this population model was developed. Population models all have diversity in them, as they are made from a population. After that, one needs to learn about each patient as an individual with respect to the behavior of digoxin in each patient. This is best done by measuring their serum digoxin concentrations, making an individualized model of the behavior of the drug in that particular patient, correlating the plots and all other data with the patient's clinical response, deciding upon a specific target goal to be achieved, and developing a maximally precise dosage regimen with which to achieve it. The population PK/PD model presented here provides the Bayesian prior for subsequent mathematically optimal open - loop feedback Bayesian adaptive control using therapeutic drug monitoring (TDM) and maximally precise dosage adjustment, as this

population model has been incorporated into the USC RightDose clinical software for optimal dosage individualization [1].

Protocols for Monitoring Serum Concentrations

It has become customary, when obtaining serum digoxin samples, to wait for a steady state, and then to obtain a sample, usually at the trough, just before a subsequent dose is to be given. The reasoning behind this strategy, to our knowledge, has never been rigorously stated or justified. It is likely that the basic reason for this custom derives from the old method of using linear regression methods to fit the logarithms of the serum concentrations. That obsolete method only works in a steady state situation, after full distribution of the drug within the body, and is not nearly as capable as the more modern Bayesian methods [5–7] to make an individualized pharmacokinetic model for a patient.

Bayesian methods will work with only a single serum sample. However, the quality and precision of the result obtained from only a single measurement is clearly suboptimal. It is often good enough for monitoring stable patients with sinus rhythm in stable situations and making reasonable adjustments to the dose. However, for best results in more acute situations such as managing patients with atrial fibrillation or flutter, it is useful to get at least one sample for each parameter value in the drug model one wishes to estimate [9,10]. The most basic pair consists generally of a peak serum digoxin concentration taken about 2 hours after a dose, and a trough before a subsequent dose. The sampling times should be recorded accurately, using military time, for example, to the nearest minute. There is no need to wait at least 6 or 8 hours after a dose before getting a serum digoxin sample. That also is an outmoded custom left over from the method of linear regression on the logarithms of the serum concentrations.

There is therefore no need to wait either for a steady state or for distribution of the drug in the body to be complete before getting a serum sample [10]. Start with the very first dose. There is no need to keep the patient at risk by not learning his/her response just as soon as possible. In addition, if needed, one might also consider getting a sample ½ hr after an oral dose, and 7 hours after either an oral or intravenous dose [11], to help determine the rate constants between the serum and the peripheral compartments. The samples do not have to be all in the same dose interval. As one acquires such data, supplemented with other samples as clinically indicated, one can analyze the patient's data as the serum results become available, make the patient's individualized Bayesian posterior model, compare the model with the patient's behavior, decide upon a target goal, and develop the multiple model dosage regimen to hit it with maximum precision (minimum expected weighted squared error). In either the serum compartment [5–7]. Or better yet, in the peripheral (effect) compartment.

Conclusion

A population pharmacokinetic and dynamic model of digoxin in adult patients with a separate peripheral effect compartment is presented, which to our knowledge is the first such model to be described for clinical use. It has been used by our laboratory for over 20 years

with good success [9]. Implications for therapeutic monitoring of serum concentrations and subsequent multiple model dosage adjustment are also presented.

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Figure 1. Estimated weighed average serum digoxin concentrations resulting from the modified ideal dosage regimen to hit a trough serum concentration of 0.9 ng/ml for the patient described above. Horizontal axis – hours into the regimen. Vertical axis - serum concentrations (ng/ml).

Figure 2.
Estimated weighted average peripheral compartment concentrations resulting from the modified ideal regimen described above. Horizontal axis – hours into the regimen. Vertical axis – peripheral compartment concentrations in ug/kg.

Figure 3.
Estimated weighted average serum digoxin concentrations resulting from the modified dosage regimen of 875 ug in 3 parts for the loading dose, followed by 125 ug daily thereafter. The weighted average trough concentration is 0.86 ng/ml at the eighth day. Lines and Axes as in Figure 1.

Figure 4.
Estimated weighted average peripheral compartment concentrations on the dosage regimen described in Figure 3A. Lines and Axes as in Figure 2.

Figure 5.

Estimated serum digoxin concentrations on the modified ideal dosage regimen to hit a trough serum concentration of 0.9 ng/ml for the 20 year old patient described in the text. Lines and Axes as in Figure 1. However, the predictions of all the population support points are shown here in addition to just the weighted average, as was shown in Figures 1–4. Here the weighted average is in the central part of the many trajectories predicted by the various population model support points in this figure.

Figure 6.

Estimated peripheral compartment concentrations resulting from the modified ideal regimen described above for the 20 year old patient described in the text. The predictions of all the population support points are shown here in addition to the weighted average, which is in the central part of the many trajectories predicted here by the various population model support points. Lines and Axes as in Figure 2.

TABLE 1

The matrix of support points for the digoxin population model.

Point #	PROB	Ka	Kcp	Kpc	Knr	Kr	Vc
1	0.0156250	0.7312000	0.6720000	0.1800000	0.0346000	0.0005510	1.8856800
2	0.0156250	0.7312000	0.6720000	0.1800000	0.0346000	0.0005510	1.2571200
3	0.0156250	0.7312000	0.6720000	0.1800000	0.0346000	0.0003510	1.8856800
4	0.0156250	0.7312000	0.6720000	0.1800000	0.0346000	0.0003510	1.2571200
5	0.0156250	0.7312000	0.6720000	0.1800000	0.0230000	0.0005510	1.8856800
6	0.0156250	0.7312000	0.6720000	0.1800000	0.0230000	0.0005510	1.2571200
7	0.0156250	0.7312000	0.6720000	0.1800000	0.0230000	0.0003510	1.8856800
8	0.0156250	0.7312000	0.6720000	0.1800000	0.0230000	0.0003510	1.2571200
9	0.0156250	0.7312000	0.6720000	0.1200000	0.0346000	0.0005510	1.8856800
10	0.0156250	0.7312000	0.6720000	0.1200000	0.0346000	0.0005510	1.2571200
11	0.0156250	0.7312000	0.6720000	0.1200000	0.0346000	0.0003510	1.8856800
12	0.0156250	0.7312000	0.6720000	0.1200000	0.0346000	0.0003510	1.2571200
13	0.0156250	0.7312000	0.6720000	0.1200000	0.0230000	0.0005510	1.8856800
14	0.0156250	0.7312000	0.6720000	0.1200000	0.0230000	0.0005510	1.2571200
15	0.0156250	0.7312000	0.6720000	0.1200000	0.0230000	0.0003510	1.8856800
16	0.0156250	0.7312000	0.6720000	0.1200000	0.0230000	0.0003510	1.2571200
17	0.0156250	0.7312000	0.4480000	0.1800000	0.0346000	0.0005510	1.8856800
18	0.0156250	0.7312000	0.4480000	0.1800000	0.0346000	0.0005510	1.2571200
19	0.0156250	0.7312000	0.4480000	0.1800000	0.0346000	0.0003510	1.8856800
20	0.0156250	0.7312000	0.4480000	0.1800000	0.0346000	0.0003510	1.2571200
21	0.0156250	0.7312000	0.4480000	0.1800000	0.0230000	0.0005510	1.8856800
22	0.0156250	0.7312000	0.4480000	0.1800000	0.0230000	0.0005510	1.2571200
23	0.0156250	0.7312000	0.4480000	0.1800000	0.0230000	0.0003510	1.8856800
24	0.0156250	0.7312000	0.4480000	0.1800000	0.0230000	0.0003510	1.2571200
25	0.0156250	0.7312000	0.4480000	0.1200000	0.0346000	0.0005510	1.8856800
26	0.0156250	0.7312000	0.4480000	0.1200000	0.0346000	0.0005510	1.2571200
27	0.0156250	0.7312000	0.4480000	0.1200000	0.0346000	0.0003510	1.8856800
28	0.0156250	0.7312000	0.4480000	0.1200000	0.0346000	0.0003510	1.2571200

Point #	PROB	Ka	Kcp	Kpc	Knr	Kr	Vc
29	0.0156250	0.7312000	0.4480000	0.1200000	0.0230000	0.0005510	1.8856800
30	0.0156250	0.7312000	0.4480000	0.1200000	0.0230000	0.0005510	1.2571200
31	0.0156250	0.7312000	0.4480000	0.1200000	0.0230000	0.0003510	1.8856800
32	0.0156250	0.7312000	0.4480000	0.1200000	0.0230000	0.0003510	1.2571200
33	0.0156250	0.4874000	0.6720000	0.1800000	0.0346000	0.0005510	1.8856800
34	0.0156250	0.4874000	0.6720000	0.1800000	0.0346000	0.0005510	1.2571200
35	0.0156250	0.4874000	0.6720000	0.1800000	0.0346000	0.0003510	1.8856800
36	0.0156250	0.4874000	0.6720000	0.1800000	0.0346000	0.0003510	1.2571200
37	0.0156250	0.4874000	0.6720000	0.1800000	0.0230000	0.0005510	1.8856800
38	0.0156250	0.4874000	0.6720000	0.1800000	0.0230000	0.0005510	1.2571200
39	0.0156250	0.4874000	0.6720000	0.1800000	0.0230000	0.0003510	1.8856800
40	0.0156250	0.4874000	0.6720000	0.1800000	0.0230000	0.0003510	1.2571200
41	0.0156250	0.4874000	0.6720000	0.1200000	0.0346000	0.0005510	1.8856800
42	0.0156250	0.4874000	0.6720000	0.1200000	0.0346000	0.0005510	1.2571200
43	0.0156250	0.4874000	0.6720000	0.1200000	0.0346000	0.0003510	1.8856800
44	0.0156250	0.4874000	0.6720000	0.1200000	0.0346000	0.0003510	1.2571200
45	0.0156250	0.4874000	0.6720000	0.1200000	0.0230000	0.0005510	1.8856800
46	0.0156250	0.4874000	0.6720000	0.1200000	0.0230000	0.0005510	1.2571200
47	0.0156250	0.4874000	0.6720000	0.1200000	0.0230000	0.0003510	1.8856800
48	0.0156250	0.4874000	0.6720000	0.1200000	0.0230000	0.0003510	1.2571200
49	0.0156250	0.4874000	0.4480000	0.1800000	0.0346000	0.0005510	1.8856800
50	0.0156250	0.4874000	0.4480000	0.1800000	0.0346000	0.0005510	1.2571200
51	0.0156250	0.4874000	0.4480000	0.1800000	0.0346000	0.0003510	1.8856800
52	0.0156250	0.4874000	0.4480000	0.1800000	0.0346000	0.0003510	1.2571200
53	0.0156250	0.4874000	0.4480000	0.1800000	0.0230000	0.0005510	1.8856800
54	0.0156250	0.4874000	0.4480000	0.1800000	0.0230000	0.0005510	1.2571200
55	0.0156250	0.4874000	0.4480000	0.1800000	0.0230000	0.0003510	1.8856800
56	0.0156250	0.4874000	0.4480000	0.1800000	0.0230000	0.0003510	1.2571200
57	0.0156250	0.4874000	0.4480000	0.1200000	0.0346000	0.0005510	1.8856800
58	0.0156250	0.4874000	0.4480000	0.1200000	0.0346000	0.0005510	1.2571200
59	0.0156250	0.4874000	0.4480000	0.1200000	0.0346000	0.0003510	1.8856800

Point #	PROB	Ka	Kcp	Kpc	Knr	Kr	Vc
60	0.0156250	0.4874000	0.4480000	0.1200000	0.0346000	0.0003510	1.2571200
61	0.0156250	0.4874000	0.4480000	0.1200000	0.0230000	0.0005510	1.8856800
62	0.0156250	0.4874000	0.4480000	0.1200000	0.0230000	0.0005510	1.2571200
63	0.0156250	0.4874000	0.4480000	0.1200000	0.0230000	0.0003510	1.8856800
64	0.0156250	0.4874000	0.4480000	0.1200000	0.0230000	0.0003510	1.2571200

TABLE 2

Summary model parameter values for the digoxin population model.

Model parameter	Mean	SD	Minimum	Maximum
Vc	1.5714	0.31428	1.25712	1.88568
Kr	0.000451	0.0001	0.000351	0.000551
Knr	0.0288	0.0058	0.023	0.0346
Kcp	0.56	0.112	0.448	0.672
Kpc	0.15	0.03	0.12	0.18
Ka	0.6093	0.122	0.1874	0.7312