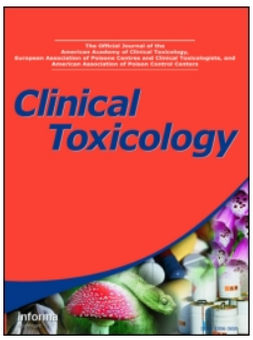

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CLINICAL RESEARCH

Physiologically based pharmacokinetic modelling of acute digoxin toxicity and the effect of digoxin-specific antibody fragments

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ABSTRACT

Context: Recommended doses of digoxin-specific antibody fragments (digoxin-Fab) for treatment of acute digoxin poisoning are pharmacokinetically unsubstantiated and theoretically excessive. Physiologically based pharmacokinetic (PBPK) modelling creates clinical simulations which are closely related to physiological and pharmacokinetic behaviour. This paper details the formulation of a PBPK model of digoxin and explores its use as a simulation tool for acute digoxin toxicity and its management.

Materials and methods: A PBPK model of digoxin was constructed and validated for acute digoxin poisoning management by comparing simulations with observed individual acute overdose patients. These simulations were compared with standard two-compartment PK model simulations.

Results: PBPK model simulations showed good agreement with post-absorption plasma concentrations of digoxin measured in 6 acute overdose patients. PBPK predictions were accurate to 1.5-fold or less of observed clinical values, proving to be more accurate than two-compartment simulations of the same patients which produced up to a 4.9-fold change. i

Conclusions: Compared to conventional two-compartment modelling, PBPK modelling is superior in generating realistic simulations of acute digoxin toxicity and the response to digoxin-Fab. Simulation capacity provides realistic, continuous data which has the potential to substantiate alternative, less expensive, and safer digoxin-Fab dosing strategies for the treatment of acute digoxin toxicity.

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digoxin; acute; toxicity; physiologically based pharmacokinetic modelling; digoxin-Fab

Context

Acute digoxin poisoning is a rare but highly lethal event, which often requires neutralisation [1]. Digoxin-Fab is an effective antidote for digoxin [2], yet current dosage guidelines for its usage during acute toxicity vary widely. Some guidelines suggest routine administration of very substantial bolus doses (up to 20 vials; total cost US$20,000) based on the calculation of total digoxin burden. This approach is expensive with many hospitals unable to stock the antidote in these amounts.

Digoxin and digoxin-Fab have very different distribution kinetics. Recommended doses of digoxin-Fab however, often attempt to match the stoichiometric body burden of ingested digoxin [3]. Digoxin is widely but slowly distributed; the volume of distribution (*V*d) of digoxin is approximately 6–8 L/kg [4]. Whereas, the *V*d of digoxin-Fab only slightly exceeds that of the extracellular fluid. The total body burden of digoxin is therefore not available for binding resulting in excretion of unbound antidote before free digoxin concentrated in the tissues diffuses back to the plasma compartment. This approach not only potentially creates unnecessary costs, but is unsafe. It risks over-neutralising the digoxin-dependent patient, while also allowing late "rebound toxicity" up to 130 h post digoxin-Fab administration in renal failure patients [5]. A smaller, titrated dosage regimen that is dependent upon observed clinical outcomes would in theory be safer, more effective, and less expensive [6].

Estimates of digoxin exposure based on concentrations and *V*d, and therefore digoxin-Fab requirements and timing, are based on concepts that are derived from a standard two-compartment pharmacokinetic model, commonly applied to guide dose adjustment in therapeutic drug monitoring. PBPK modelling is a method that more closely reflects the actual mechanisms of the body and allows for extrapolation outside the studied population and experimental conditions [7,8]. PBPK modelling is more detailed than the standard two-compartment model, which provides only one rate constant to describe the rate of distribution and rate of rebound of plasma digoxin after neutralisation from all tissues (despite the massive variation in organ blood flow and tissue perfusion that determines these processes in individual organs). PBPK model simulation can provide an estimation of the pharmacokinetics that underlies plasma concentration changes during digoxin toxicity with more accuracy than conventional methods. In particular, PBPK modelling should provide a better understanding of the time course of acute digoxin poisoning in the presence of digoxin-Fab treatment.

This paper details the formulation of a PBPK model of digoxin and the assessment of its use as an accurate

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Supplemental data for this article can be accessed here.

Table 1. Pharmacokinetic input parameters for PBPK model.

Parameter	Value	Reference/Notes
Digoxin		
Michaelis-Menten maximum absorption velocity (vmax) (nmol/hr)	3500	Experimental
Michaelis-Menten Constant (km) (nmol)	2000	Experimental
Fractional bioavailability (F)	0.80	[4]
Fraction unbound in plasma	0.71	[15]
Molecular weight (Da)	780.963	[4]
Human blood: plasma ratio (BPR)	0.83	[12]
Hepatic Clearance (CL_H) (mL/kg/min)	0.80	[16]
Digoxin-Fab		
Molecular weight (Da)	46000.0	[20]
Human blood: Plasma ratio (DFBPR)		
Male	0.554	Based upon human packed cell volume (PCV) [17]
Female	0.586	
Diffusion constant (FDC)	0.195	Experimental
Total clearance (% of body weight)	0.32	[5]

Table 2. Physiological input parameters for PBPK model of digoxin.

Compartment	Tissue: Plasma Partition coefficients (P_T)	Regional Blood Flow Distribution (% of cardiac output)	Tissue Volume (% of body weight)
Heart	7.350000	0.040	0.004
Muscle	7.350000	0.191	0.430
Adipose	10.80000	0.052	0.200
Brain	1.462328	0.114	0.020
Bone	1.284329	0.042	0.160
Kidney	0.9264303	0.175	0.005
Liver	1.130881	0.227	0.023
Skin	0.9264303	0.058	0.110
Remaining compartment	8.000000	0.101	0.010

References: [15, 20–23].

simulation tool for estimating digoxin plasma concentration in acute digoxin toxicity following treatment with digoxin-Fab.

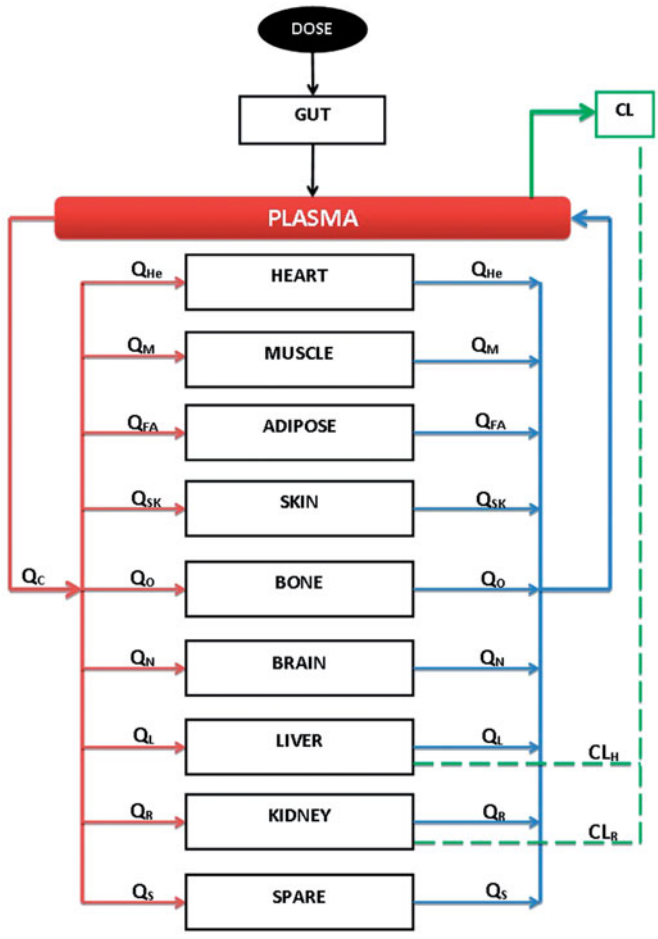

Figure 1. Schematic diagram of the PBPK model of digoxin. Oral absorption of digoxin from the gut was determined by Michaelis–Menten absorption kinetics and was added directly into circulation. Whole-body distribution of digoxin was perfusion-limited. Venous return was also dependent upon tissue blood flows. Metabolic and renal clearance were modelled directly from the circulation so that clearance could be easily altered for the addition of digoxin-Fab to the system.

Materials and methods

We created and validated a PBPK model of digoxin in the following sequence [9]:

1. A PBPK model for oral administration of digoxin was built using physiological data obtained from the literature and previous PBPK modelling studies (Table 1 and 2). Ordinary differential equations (ODEs) were constructed to simulate the effect of addition of digoxin-Fab to the system.
2. The model was initially validated by comparison with published digoxin pharmacokinetic studies (Supplementary Material D).
3. The model was validated for acute digoxin poisoning and digoxin-Fab administration by comparing several, individual PBPK model simulations of acute overdose with measured plasma digoxin levels.
4. We compared simulations in the PBPK model to those generated with a two-compartment model of digoxin [6].

Model development

The modelling software package Berkeley Madonna™ (version 8.3.18; University of California, Berkeley, CA, USA) was used for both coding and simulations of the PBPK model.

The PBPK model was constructed using a "bottom up" approach which incorporated physiological and pharmacokinetic considerations for the uptake of digoxin in the body. The whole-body model consisted of ten singular compartments representing the plasma, heart, muscle, adipose tissue, brain, bone, skin, liver, kidney, and remaining volume of distribution (spare). Each compartment was supplied by the central plasma compartment and in turn, venous returns supplied the central plasma compartment (Figure 1).

Gastrointestinal absorption of digoxin was modelled as a saturable process [10–12] using Michaelis–Menten (MM) kinetics. The maximum absorption velocity and MM constant were determined using the BM slider function as the model describes digoxin pharmacokinetics in terms of amount rather than concentration.

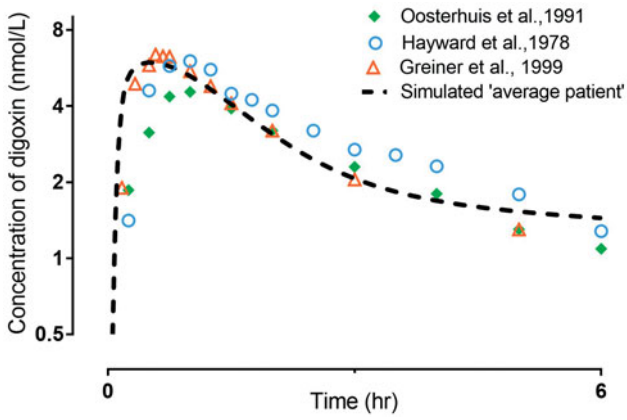

Figure 2. Example of PBPK model verification studies for 1 mg oral digoxin doses. Symbols are observed mean patient values from three volunteer studies [24–26]. Dotted line represents a PBPK simulation of the "average patient" from all three studies.

The remaining model was constructed using generic PBPK code [13]. Perfusion-rate limited kinetics that are dependent upon the individual proportion of blood flow to each organ and the plasma partition coefficients at each organ site were used to model the distribution of digoxin. Further details on the construction of model and subsequent code can be found in Supplementary Materials A and B.

Model parameterisation

Pharmacokinetic and physiological parameters for the model were sourced from the literature (Table 1 and 2). Physiological parameters were customised, where possible, to the individual patient to enhance simulation accuracy.

Specific details of sources of data are included in Supplementary Materials C and E.

Validation of the PBPK model

The completed model was initially validated by simulating an "average healthy patient" described within thirteen published therapeutic digoxin pharmacokinetic studies and comparing it to the measured mean population values in these studies. Further details of these simulations are reported in Supplementary Material D.

Validation of model in acute digoxin poisoning

Patient data used for simulation of toxicity came from the "Digoxin Overdose and Response to Antibody (DORA)" Project, described in more detail elsewhere [14]. Six patients were recruited from hospitals in New South Wales and Queensland following an acute digoxin overdose. This study has ethical approval in both NSW and QLD. There were three male and three female patients ranging from 34–91 y.

Berkeley Madonna (University of California, Berkeley, U.S.A) was used to simulate the six acute digoxin overdose scenarios, including the impact of digoxin-Fab on concentrations of free digoxin. The age, sex, ideal body weight, heart rate on admission, and serum creatinine levels, reported time of digoxin overdose, ingested amount, time of digoxin-Fab administration, and dosage of digoxin-Fab for each patient were the key inputs (Supplementary Table 3).

The results of the simulations of each patient were compared to their measured plasma free digoxin concentrations at varying time points pre- and post-digoxin-Fab administration. The comparison aimed to analyse the ability of the model to realistically imitate the time course of clinical events, as opposed to an exercise in data fitting. No distribution parameter optimisation was performed (or apparently required).

Comparison of PBPK modelling of digoxin with two-compartment model

We also simulated concentration-time profiles of the same acute digoxin toxicity patients using a two-compartment model [6] which employed the same MM absorption kinetics as the PBPK model. The results of these simulations were evaluated by visual inspection, and agreement with observed values, compared to the concentration-time profiles generated by the PBPK model. By comparing the two methods, the theoretical benefit of using the more detailed PBPK approach to modelling digoxin toxicity could be tested to support the use of the most accurate modelling technique in future clinical studies.

Results

Simulations of digoxin pharmacokinetics in humans

The PBPK model was first validated by comparing simulated concentration-time profiles of digoxin with observed values found in the literature. Figure 2 compares the simulation of the concentration-time profile of digoxin in an "average patient" with mean patient data from three PK studies of a single, oral dose of 1mg digoxin. More details of these validation studies can be found in Supplementary Material D.

PBPK simulations of digoxin toxicity and digoxin-Fab treatment pharmacokinetics

Simulations of six acute overdose patients recruited for the DORA study were then performed. In Figure 3 digoxin plasma concentration-time profiles of four patients were compared with plasma digoxin levels collected from the patients during presentation. The four patients were selected for comparison due to more digoxin levels collected from them, which represented the post-digoxin Fab administration rebound effect – a key aspect of clinical digoxin toxicity to be accurately modelled. The patient data which was used for simulation and simulations of the other two acute toxicity patients from the DORA study are included in Supplementary Material E.

Upon inspection, figure 3 demonstrates a good agreement between simulated and observed digoxin concentrations. The inserted scatter plots represent a significant

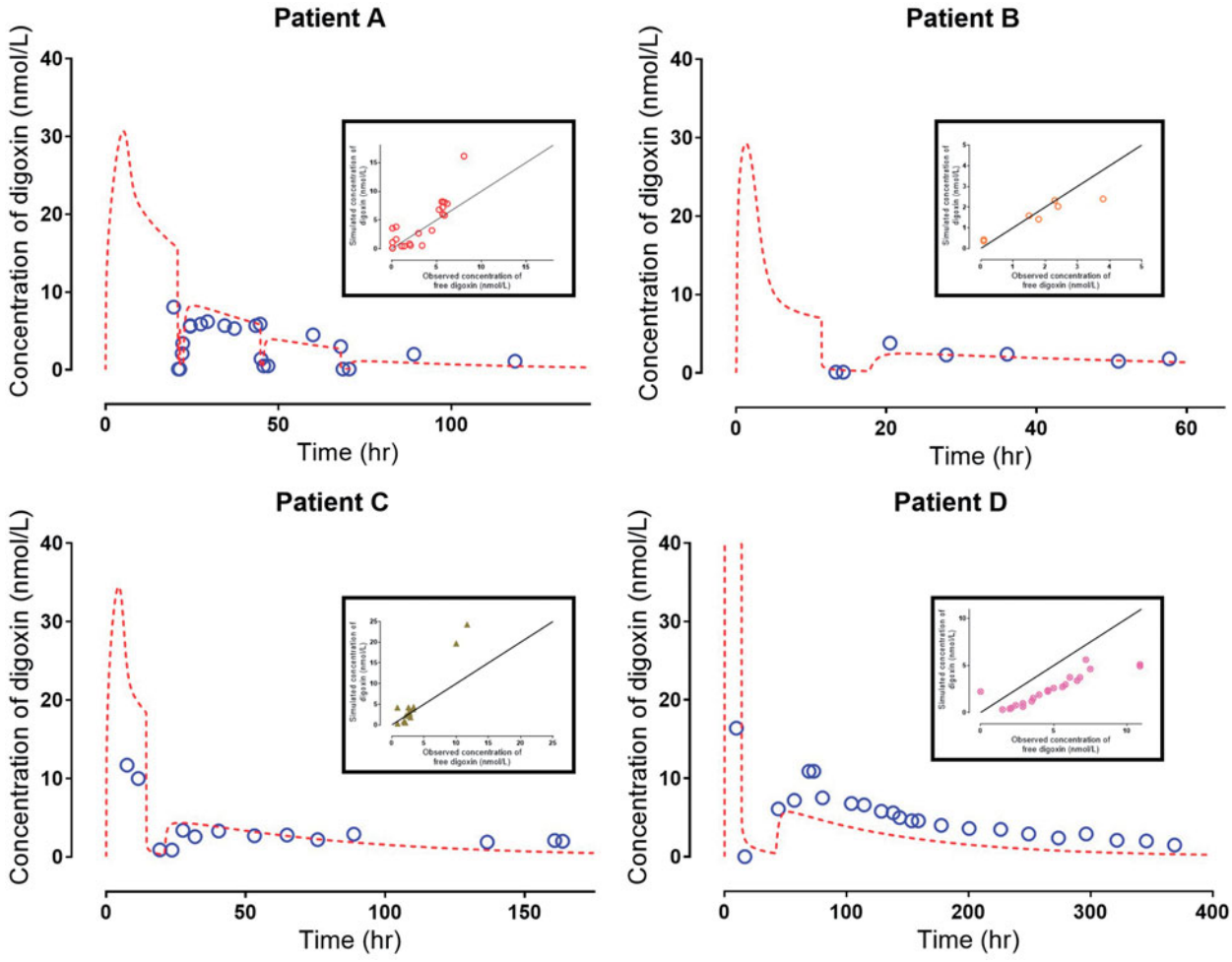

Figure 3. PBPK simulated concentration-time profiles of acute digoxin overdose patients and measured concentrations following titrated doses of digoxin-Fab. The dotted line represents simulated concentration time profiles generated by the PBPK model for each patient. Open circles represent the plasma concentration of digoxin measured in each patient at different times. Inserts contain scatter plots which represent the agreement between observed and simulated patient concentrations of free digoxin. Patient A: 43 years, male ingested an overdose of 13.5 mg. He received digoxin-Fab infusions at 20.8 (80 mg), 21.5 (80 mg), 44.8 (40 mg), and 68 (40 mg) hours post-reported overdose time. Patient B: 34 years, female ingested an overdose of 4.1 mg. She received one digoxin-Fab infusion at 11.3 (80 mg) hours post-reported overdose time. Patient C: 69 years, male ingested an overdose of 12.5 mg. He received digoxin-Fab infusions at 14.37 (80 mg), 14.50 (80 mg), 14.92 (80 mg), and 15.42 (80 mg) hours post-reported overdose time. Patient D: 61 years, male ingested an overdose of 25 mg. He received one digoxin-Fab infusion at 14 (800 mg) hours post-reported overdose time.

Table 3. Comparison of the area under the curve accuracy of the PBPK model and two-compartment model.

Patient	PBPK model			Two-compartment model		
	Observed AUC	*Simulated AUC*	*AUC accuracy*	*Observed AUC*	*Simulated AUC*	*AUC accuracy*
A	263.2	272.9	1.0	263.2	730.4	2.8
B	94.14	81.41	0.86	94.14	208.2	2.2
C	436	464.1	1.1	436	1454	3.3
D	1538	1058	0.69	1538	7575	4.9

positive correlation between observed values and values generated by the model in patient A ($r = 0.855$; $p < 0.0001$), patient B ($r = 0.943$; $p = 0.002$), patient C ($r = 0.973$; $p < 0.0001$), and patient D ($r = 0.716$; $p = 0.001$).

Prediction accuracy of the PBPK model was determined by comparing the area under the curve (AUC) of observed and predicted concentration-time curves (Table 3). A 1.25-fold change in AUC was determined as a safe window of prediction as a wider window of prediction could have dangerous clinical repercussions in the setting of digoxin toxicity [15]. Three of the four PBPK simulations were within a fold change of 1.2. The predicted AUC of patient D produced a 1.5-fold change.

The simulated concentration profile follows the pattern of acute overdose prior to digoxin-Fab administration yet overestimates the early values. This could be due to toxic (vagal) effects on gastrointestinal motility, vomiting and administration of charcoal; none of which we attempted to include in the simulated model. The overestimation does not however, seem to affect the accuracy of the model following digoxin-Fab administration.

Two-compartment simulations of digoxin toxicity and digoxin-Fab treatment pharmacokinetics

Simulations generated by a two-compartment model, compared with collected plasma digoxin levels of the same four patients, are shown in Figure 4.

There was a positive correlation between two-compartment simulated free plasma digoxin levels and observed values in patient A ($r = 0.8125$; $p < 0.0001$), patient B ($r = 0.8682$; $p = 0.0113$), patient C ($r = 0.9163$; $p < 0.0001$), and patient D ($r = 0.8943$; $p < 0.0001$).

However, compared to the PBPK model, simulations generated by the two-compartment model were less congruent with observed values. The two-compartment model consistently overestimated the plasma concentration of digoxin post digoxin-Fab administration in the rebound phase. All of the two-compartment simulations predicted an AUC fold change greater than 1.25, with AUC prediction ranging from a 2.2 to 4.9-fold change (Table 3). Both models however, overestimate early concentrations in the absorption phase (i.e., rate of absorption).

Discussion

Clinicians implicitly or explicitly use simple pharmacokinetic models whenever they estimate neutralisation doses of digoxin-Fab from digoxin concentrations. These assume redistribution will be fairly rapid. This leads to expensive strategies that fail to prevent substantial rebound. The key to efficient and cost-effective dosing is to avoid mismatch between timing of digoxin Fab and the redistribution of digoxin back into the circulation, where it has toxic effects. Compared to conventional two-compartment PK simulations, PBPK modelling was superior in generating realistic simulations of acute digoxin toxicity before and after treatment with digoxin-Fab including accurate prediction of rebound concentrations post digoxin-Fab. This may be useful for exploring a range of dosing strategies for digoxin-Fab, and how these might be modified by a range of patient and poisoning related factors. These strategies could then feasibly be evaluated in acute digoxin poisoning patients. It is apparent from the patients included in this study that digoxin-Fab doses much less than those required for full or half neutralisation (based on either the dose or concentration) were sufficient to reduce free digoxin concentrations close to the therapeutic range, and conversely large bolus doses of digoxin-Fab did not prevent substantial rebound as was seen in Patient D.

Strengths and weaknesses of the study

Initial PBPK model validation using therapeutic doses

Discrepancies exist between the independent studies used for validation and the simulations produced. This can be accounted for by the limited, averaged parameters, and results of the patient groups provided by each paper for input into the model. Neither the average patient nor average observed values reflect realistic, individual physiology that the PBPK model attempts to emulate; thus, pre-emptive assessment of the model's ability was difficult to ascertain. Additionally, the validation studies used small patient groups that predominantly comprised of healthy, young, male volunteers. Our ability to comprehensively verify the model for various populations was therefore limited.

Validation of PBPK simulations of acute digoxin poisoning patients

The simulations aimed to precisely mimic the physiological and logistical conditions experienced by each acute digoxin overdose patient. This strategy was limited as it was dependent on recordings by hospital staff and the ability of each patient to accurately recall time of overdose and dosage (if at all). Incongruence between observed and predicted digoxin concentrations therefore may be partially attributed to errors in data recording.

PBPK model physiological parameters

A PBPK model's strength lies in its greater attention to physiological factors. Physiological parameters including tissue volumes, regional blood flow distribution, kidney, and liver function were calculated using equations that are dependent upon individual patient measurements. These tailored parameters increased the validity of the model, but meant assumptions had to be made when certain measurements were not included in collected patient data. Less than 50% of the patients had a recorded body weight. Considering this ambiguity in the data and the use of the Cockcroft–Gault equation for kidney function, ideal body weight was instead calculated for each patient. Tissue volume and clearance values were both dependent upon this measurement.

The model employs perfusion rate limited kinetics [13] where blood flow distribution is the limiting process. Total cardiac output was calculated as the product of patient heart rate and stroke volume. The heart rate of the patient measured prior to digoxin-Fab administration and the mean population stroke volumes were used. This reduced physiological accuracy of simulations as heart rate is not stable during toxicity. Similarly, kidney clearance was modelled using initial creatinine levels only; again this value is not static, thus, limiting physiological precision.

The PBPK code for absorption was simplistic. The gastrointestinal tract (GIT) was treated as a single, well-stirred compartment with uniform absorption determined by Michaelis–Menten absorption kinetics. More detailed PBPK absorption models are possible but are complex [15]. Such models have not yet been shown to improve prediction of concentrations in overdose, where factors such as vomiting and charcoal administration play important roles. We did not have enough early concentrations to directly evaluate alternative overdose absorption models and thus, chose to use a Michaelis–Menten absorption equation based on the assumption that digoxin absorption from the GIT is a saturable process[11,12].

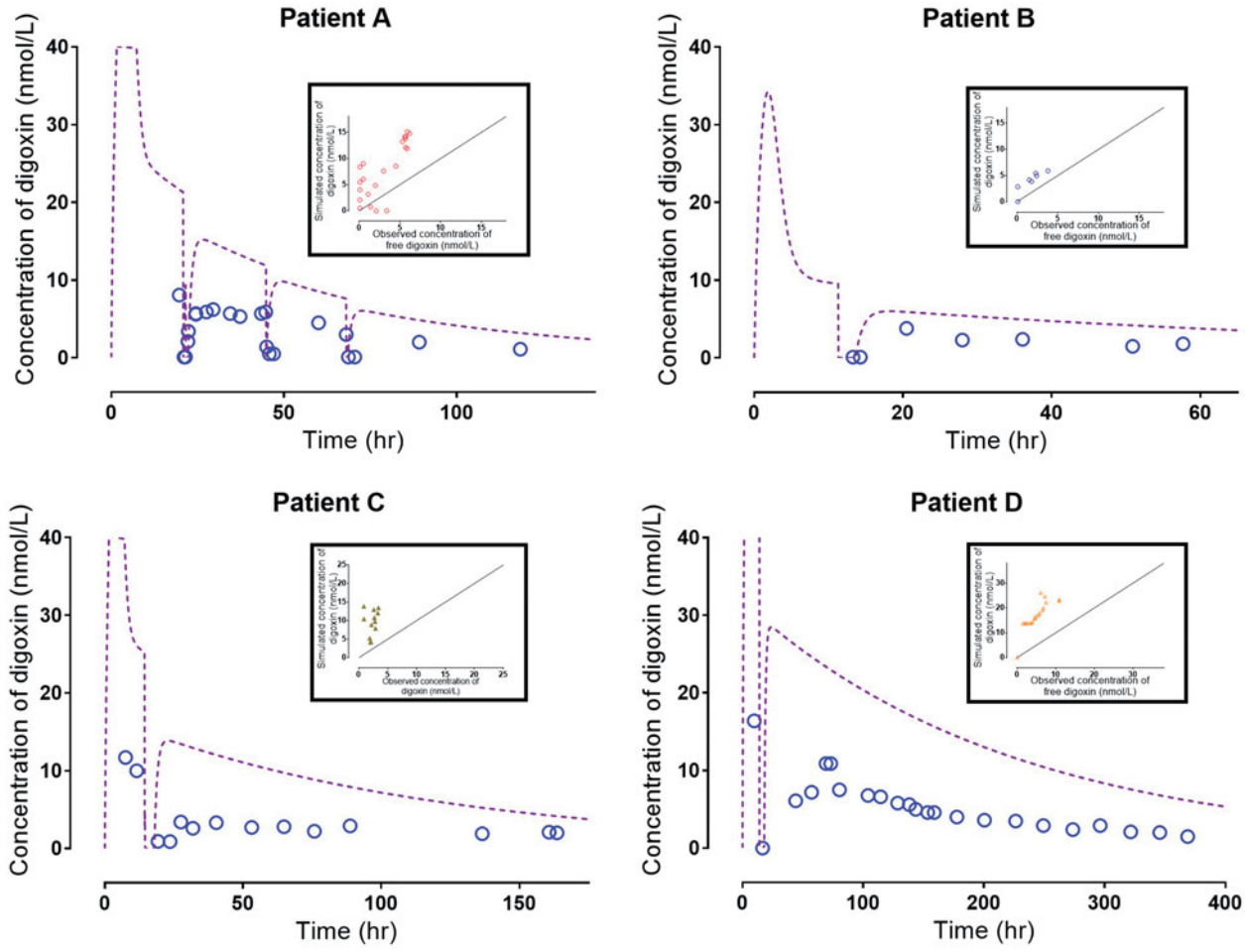

Figure 4. Two-compartment simulated concentration-time profiles of acute digoxin overdose patients and measured concentrations following administration of digoxin-Fab. The dotted line represents simulated concentration-time profiles generated by the two-compartment model of each patient. Open circles represent the plasma concentration of digoxin measured in each patient at different times. Inserts contain scatter plots which represent the agreement between observed and simulated patient concentrations of free digoxin. Patient A: 43 years, male ingested an overdose of 13.5 mg. He received digoxin-Fab infusions at 20.8 (80 mg), 21.5 (80 mg), 44.8 (40 mg), and 68 (40 mg) hours post-reported overdose time. Patient B: 34 years, female ingested an overdose of 4.1 mg. She received one digoxin-Fab infusion at 11.3 (80mg) hours post-reported overdose time. Patient C: 69 years, male ingested an overdose of 12.5mg. He received digoxin-Fab infusions at 14.37 (80 mg), 14.50 (80 mg), 14.92 (80 mg), and 15.42 (80 mg) hours post-reported overdose time. Patient D: 61 years, male ingested an overdose of 25mg. He received one digoxin-Fab infusion at 14 (800mg) hours post-reported overdose time.

The PBPK simulations indicate probable overestimation of the rate of absorption in acute digoxin overdose, illustrating the difficulties with this aspect of the model. The motivation of this study however, was to simulate acute toxicity post absorption, particularly the post digoxin-Fab rebound phase. Considering simulations were able to accurately replicate this phase, our simple formulation for GIT absorption was not detrimental to overall results produced. However, a much better absorption model has to be developed to usefully explore gastrointestinal decontamination techniques.

Total clearance of digoxin was modelled as the sum of hepatic and renal clearance rates that removed digoxin directly from the central plasma compartment independent of cardiac output. Hepatic clearance of digoxin was calculated simply as proportional to body weight (Table 1). Renal clearance of digoxin was assumed to be equal to creatinine clearance [16] hence was calculated using the Cockcroft–Gault equation. This approach was limited, as it does not directly estimate the percent of plasma protein binding (reducing glomerular filtration) or the tubular secretion component of digoxin elimination. However, these two factors generally balance each other out in therapeutic use and we had no basis to speculate how these might be altered in overdose.

Modelling digoxin clearance directly from the plasma compartment is not physiologically consistent; however initial simulations for model validation showed predicted plasma concentrations were not significantly affected by this assumption. This was advantageous in that additional total clearance of digoxin due to digoxin-Fab binding could be easily modelled from within the plasma compartment.

The model's compartment structure is physiologically-limited. Ideally, the PBPK model would contain a compartment for each tissue. Practically for digoxin pharmacokinetics however, only eight major tissue compartments were required outside the plasma compartment. All other tissues were clumped into a "spare" compartment to make up the remainder of the volume of distribution. This compartment, though physiologically undetailed, had no major detrimental impacts upon simulations.

PBPK model pharmacokinetic parameters

The biological plausibility of the simulations is influenced by the pharmacokinetic parameters input. Tissue to blood partition ratios and the blood to plasma ratio were collected from previously verified pharmacokinetic studies of digoxin [15,17].

The model implemented the assumption that binding of digoxin to digoxin-Fab molecules occurs at a 1:1 ratio. This approach had limited substantiation as the actual binding kinetics of digoxin and digoxin-Fab at the molecular level has not yet been studied closely.

The rate used to describe the influx of digoxin back from the tissues to the central compartment accounts for both the dissociation of digoxin from ATPase and the diffusion of non-bound digoxin from the tissue site. Using this rate the model was able to replicate the observed rebound effect suggesting that this approach, albeit its simplicity, is effective. The success of this technique, may suggest that the rate of dissociation from the binding site has a negligible effect on the rate of diffusion back into the central compartment. Currently, there are no radio-labelled studies to suggest otherwise.

Results within the context of previous studies

There are only two other previously formulated PBPK models of digoxin within the literature [12,15]. Unlike this study, which used generic software and code, the previously developed PBPK models were constructed using commercial platforms; the Simcyp Population-Based Simulator (Certara, NJ, U.S.A) and PKSIM. Development of the model was heavily influenced by these previous studies and they formed a basis for its structure and parameterisation.

There has been a growing interest in PBPK modelling within the pharmaceutical industry for use within drug development and safety assessment [13]. Previous digoxin PBPK models had similar applications investigating digoxin drug–drug interactions. [12,15]. This was in contrast to this study which was focused on clinical toxicological applications of PBPK modelling to investigate acute digoxin poisoning.

The previous PBPK models of digoxin simulated large, virtual populations under specific dosage and demographic conditions. For this study, modelling was instead used to simulate individual patients with observed dosages and treatment responses. Simulations at a smaller, more detailed scale were advantageous for motivations of this particular study as they were more reflective of the clinical setting. Other differences between previous PBPK digoxin studies and this study can be found in Supplementary Material F.

Overall, despite different motivations, previous research combined with this study demonstrates that PBPK modelling is a viable predictive tool for investigating the pharmacokinetics of digoxin.

Possible implications of this study

PBPK modelling accurately simulated concentration-time profiles of digoxin toxicity in the presence of digoxin-Fab treatment. PBPK modelling improved upon conventional two-compartment modelling, particularly with respect to the rate of redistribution (rebound). These techniques can now be used to simulate the full range of acute overdose scenarios and patients where digoxin-Fab might be used. A key issue with substantial consequences for antidote effectiveness, availability, and cost is whether a more conservative, titrated approach to dosage of digoxin-Fab would be equally effective, or even superior to large boluses calculated to neutralise the estimated total body burden [6,18]. PBPK simulation of this titrated dosage approach used with Patient A was accurate (Table 3). Most labs are unable to measure the free plasma concentration of digoxin following digoxin-Fab administration. This accuracy suggests that in the future, the PBPK model could be used to further substantiate and assist the titrated dosage approach including timing of dosages through its unlimited simulation capacity. This would provide strong indirect evidence to support recent changes to digoxin-Fab dosage recommendations suggested by various groups [19].

Conclusion

PBPK modelling has not been previously applied within the context of acute digoxin toxicity. This study has shown that individualised PBPK modelling is a useful tool for predicting digoxin concentration-time profiles that improves upon two-compartment methods. PBPK modelling provides a novel research platform through which multiple digoxin overdose treatment scenarios including acute, and potentially chronic, overdose can be rapidly and reliably investigated.

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Disclosure statement

The authors have no declaration of interest to report. The authors alone are responsible for the content and writing of the paper.

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