Comparing paediatric intravenous phenytoin doses using physiologically based pharmacokinetic (PBPK) modelling software

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Highlights

- IV loading doses of phenytoin (18 and 20mg/kg) were modelled in children age 2-10 years
- Therapeutic concentrations were similar for each dose (62% 18mg/kg v 59% 20mg/kg)
- Most variation was due to individual factors, not dose related
- The dosing regimen proposed by the BNFc appears appropriate

Abstract

Purpose

To use a physiologically-based pharmacokinetic (PBPK) modelling system to predict the serum levels achieved by two different intravenous loading doses of phenytoin.

Methods

A phenytoin pharmacokinetic model was used in the Simcyp™ population-based ADME simulator, simulating 100 children age 2-10 years receiving intravenous phenytoin (18 and 20mg/kg). Visual checks were used to evaluate the predictive performance of the candidate model.

Results

Loading with doses of 18mg/kg, blood levels were sub-therapeutic in 22/100 (concentration at 2 hours post infusion (C_{2h}) <10µg/mL), therapeutic in 62/100 (C_{2h} 10-20µg/mL), and supra-therapeutic in 16/100 (C_{2h} >20µg/mL). Loading with 20mg/kg, the percentages were 15, 59, and 26 respectively. Increasing from 18mg/kg to 20mg/kg increased the mean C_{2h} from 16.0µg/mL to 17.9µg/mL, and the mean AUC from 145 to 162µg/mL/h. A C_{2h} >30µg/ml was predicted in 4% and 8% of children in the 18mg/kg and 20mg/kg doses, with 3% predicted to have a C_{2h} >40µg/mL following either dose.

For maintenance doses, a 1st dose of 2.5 or 5mg/kg (intravenous) given at 12 hours (after either 18 or 20mg/kg loading) gives the highest percentages of 10-20µg/mL serum concentrations. For sub-therapeutic concentrations following intravenous loading (20mg/kg), a 1st maintenance dose (intravenous) of 10mg/kg will achieve therapeutic concentrations in 93%.

Conclusions

Use of PBPK modelling suggests that children receiving the 20mg/kg intravenous loading dose are at slightly increased risk of supra-therapeutic blood levels. Ideally, therapeutic drug monitoring is required to monitor serum concentrations, although the dose regime suggested by the BNFc appear appropriate

11th October 2015

Comparing paediatric intravenous phenytoin doses using physiologically based pharmacokinetic (PBPK) modelling software

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DH and HB conceived the study. HB analysed the data, RA provided clinical correlation, DH, RA and HB all wrote and edited the manuscript.

Introduction

The recommended intravenous loading dose of phenytoin in the treatment of paediatric convulsive status epilepticus (CSE) in the UK was increased from 18mg/kg to 20mg/kg in January 2011, to reduce the theoretical risk of miscalculation (1). Phenytoin has a narrow therapeutic range (10-20 µg/ml) and non-linear pharmacokinetics (2), such that at high concentrations phenytoin exhibits zero order kinetics in man (linear increase and decrease in serum concentrations at higher dosages secondary to saturation of metabolising enzymes). Consequently, toxic levels may take longer to clear than most other drugs which exhibit first order kinetics at all concentrations (3).

Subsequent analysis of phenytoin levels taken in routine clinical practice has shown that the 20mg/kg loading results in a similar percentage of supra-therapeutic serum concentrations compared with 18mg/kg, but with a higher observed rate of clinical toxicity (4). At their most severe, phenytoin toxicity can include potentially fatal cardiac arrhythmias, hypotension and neurological side effects and particularly at higher serum concentrations (5).

Phenytoin metabolism is affected by concomitant medication by a number of factors including obesity, concomitant medications, and pharmacogenomic variation in CYP2C9 and CYP2C19 (6-9), and significant inter-individual variability in the pharmacokinetics has been noted in children (10).

The SimCYP population-based ADME simulator software allows mechanistic-modelling and simulation of the processes involved in drug absorption, distribution, metabolism and excretion. A unique feature of this simulation software is its ability to provide not just outputs based on an 'individual' but also outputs from individuals within a population (11). This has been used in paediatric populations to successfully model the pharmacokinetics of numerous medications (12, 13).

The SimCYP software was used to model the outcomes of both the 18mg/kg and 20mg/kg intravenous loading doses of phenytoin. This included an evaluation of the likelihood of supra- (>20µg/mL) and sub- (<10µg/ml) therapeutic levels associated with the two doses and an attempt to determine the optimal timing of additional treatment with phenytoin (if required clinically). Current clinical practice in our institution is to measure the total serum phenytoin concentrations between 1 and 3 hours following completion of the infusion of the intravenous

loading dose. The modelling mimicked this practice and concentration values at 2 hours post-loading dose are reported as a representative value.

Methods

SimCYP model inputs

A previously reported phenytoin pharmacokinetic model was used in the SimCYP™ population-based ADME simulator (V14; SimCYP Limited, Sheffield, UK) (14). The applicability of this model to use in children was assessed by comparison to clinical data from children as reported by the authors previously (4, 15). Hawcutt et al [15] reported on pharmacokinetic data following intravenous phenytoin administered as an 18 mg/kg loading dose in children and a subsequent report was provided by Piper et al [4]following dosing at 20 mg/kg. These papers reported phenytoin concentrations at time-points of 60-180 minutes post administration of phenytoin and calculated the percentage that were within the therapeutic reference range (10-20 µg/mL) sub-therapeutic (<10 µg/mL) and supra-therapeutic (<20 µg/mL). A simulated trial to replicate the dosing reported by these studies was created within the software. Visual checks were used to evaluate the predictive performance of this model.

The simulation was performed in a population of 100 individuals aged from 2-10 years.

This model was interrogated to determine:

- What proportion of children achieved therapeutic concentrations (C_{2h} at 2 hours post infusion) of phenytoin (10 to 20 µg/mL) when given either 18mg/kg or 20mg/kg loading dose?
- What is the population mean C_{2h} concentration at 2 hours for each dose?
- What is the population mean 'Area Under the Curve' (AUC [0-12 hours]) for each dose?
- What proportion of children will have a C_{2h} at 2 hours post dose >30µg/mL or C_{2h}>40 µg/mL?

- When is the optimal time to administer the first maintenance dose following completion of the initial loading dose (20mg/kg) to avoid drug accumulation and supra-therapeutic concentrations with potential clinical toxicity?
- Can these data assist with clinical decisions regarding intravenous maintenance dosing in children with sub-therapeutic levels of phenytoin?

Results

Loading doses

The simulated pharmacokinetic profiles of intravenous phenytoin loading doses for 100 individuals aged from 2-10 years were created at doses of both 18 and 20 mg/kg. The mean concentrations together with the 95% confidence intervals are shown in Figure 1.

The concentration of the medication 2 hours post-infusion (C_{2h}) was simulated in the population. The 18 mg/kg dose resulted in 62% of the population achieving the therapeutic reference range (10-20 µg/mL); 16% of the population achieved plasma concentrations >20 µg/mL; and 22% did not achieve the 10 µg/mL level. The 20mg/kg dose resulted in 59% of population achieving the therapeutic reference range; 26% of the population achieved plasma concentrations >20 µg/mL; and 15% did not achieve the 10 µg/mL level. Overall, an increase in dose from 18mg/kg to 20mg/kg increases the mean C_{2h} from 16.0µg/mL to 17.9 µg/mL (Figure 2A).

Limited pharmacokinetic data following intravenous phenytoin in children administered as a 18 mg/kg loading dose infused over 20 minutes has been reported previously (15).

The modelled pharmacokinetics of phenytoin matched favourably to the clinical data dosed at 18mg/kg reported by Hawcutt et al [15]; the average C_{2h} value was 16.0µg/mL for the modelled data and the mean Cmax value reported from the clinical data was 15.3 µg/mL. Seventy seven per cent of phenytoin concentration levels were within the therapeutic reference range in the patient population compared to 62% in the model; 3 % of patients were sub-therapeutic (22% in the model) and 19% of patients were supra-therapeutic (16% in the model) (15). The main difference between the model and the reported clinical data was the number of sub-therapeutic values observed at 2 hours.

A comparison of the model and the clinical data reported at 20 mg/kg (4) showed a similar trend; 79% of phenytoin concentration values in the patient population were within the therapeutic reference range (59% modelled population); 0 % patients were sub-therapeutic (15% modelled) and 21% patients were supra-therapeutic (26% modelled) (4). The model showed an increase in the percentage of supra-therapeutic plasma concentrations similar to that reported in the clinical data. However there were many more sub-therapeutic levels observed in the modelled data.

Comparison of the AUC values, minimum, 5th centile, mean, 95th centile and maximum values for each population is shown in Figure 2B. The increase in dose increases the AUC value for the first 12 hours following the infusion from 145 µg/mL/h to 162 µg/mL/h.

An evaluation was undertaken of those children that had very high blood level at both doses. Using the modelled 18mg/kg intravenous loading dose, 4% had dose levels greater than 30 µg/mL; 3% had levels greater than 40 µg/mL. Using the modelled 20mg/kg dose level 8% had dose levels greater than 30 µg/mL; 3% had levels greater than 40 µg/mL.

Maintenance Doses

The effects of the time of the administration of the first maintenance dose were evaluated for 18mg/kg and 20mg/kg loading doses. A second simulation was run to include a subsequent intravenous maintenance dose given at 12 hours following the loading dose (18mg/kg or 20mg/kg). The mean profiles are shown in Figure 3.

The percentage of individuals within the second simulation in whom the next Cmax (concentration immediately following the first maintenance dose) were lower, within, or higher than the therapeutic reference range is reported in Table 1 for a range of maintenance doses. The maintenance doses which produces the greatest of the simulated population whose second Cmax value is within the target therapeutic reference range of 10 -20 µg/mL when administered 12 hours following the loading dose is 5mg/kg (following an 18mg/kg loading dose) and 2.5mg/kg (following a 20mg/kg loading dose) (Table 1).

	The percentage of populations simulated Cmax values following an intravenous maintenance dose 12 hours following the loading dose					
	18mg/kg			20mg/kg		
Maintenance dose administered	<10 µg/mL	10-20 µg/mL	>20 µg/mL	<10 µg/mL	10-20 µg/mL	>20 µg/mL
2.5 mg/kg	31	63	6	27	63	10
5.0 mg/kg	20	66	14	16	62	22
7.5 mg/kg	11	59	30	7	58	35

Table 1. Frequency of individuals with a Cmax value within or outside the range 10-20 µg/mL following a maintenance dose of either 2.5, 5 or 7.5 mg/kg.

Further interrogation of the data was undertaken in the subgroup of the population in which the initial phenytoin concentration was less than 10 µg/mL at 2 hours after the loading dose. Predictably, the proportion in which the levels were less than 10 µg/mL at 12 hours following a maintenance dose decreased as the maintenance dose increased, and the model was able to quantify the proportions at, above or below the therapeutic reference range for a range of maintenance doses. At 18mg/kg, 22 subjects had plasma levels of less than 10 µg/mL at 2 hours; of these 21 (95%) were below 10 µg/mL at 12 hours following a 2.5 mg/kg maintenance dose; 17 (77%) with a maintenance dose of 5 mg/kg; 11 (50%) with a maintenance dose of 7.5 mg/kg and 6 (28%) with a maintenance dose of 10 mg/kg. At 20mg/kg, 15 subjects had plasma levels less than 10 µg/mL at 2 hours; of these all 15 (100%) were below 10 µg/mL at 12 hours following a 2.5 mg/kg maintenance dose; 14 (93%) with a maintenance dose of 5 mg/kg; 11 (47%) with a maintenance dose of 7.5 mg/kg and 1 (7%) with a maintenance dose of 10 mg/kg.

These data indicate that subjects with a low level of phenytoin at 2 hours are likely to require a higher maintenance dose to achieve a level within the therapeutic reference range. None of those who achieved sub-therapeutic levels at 2 hours achieved supra-therapeutic levels at 12 hours and therefore the risk of using a higher initial maintenance dose is low according to this simulated trial.

Discussion

The management of convulsive status epilepticus in children in the UK changed in 2012 with the increase in the loading dose of intravenous phenytoin from 18 to 20mg/kg. Audits were undertaken to evaluate the blood levels of phenytoin before and after this increase [4,15]. These data were limited by the sample size available, but overall little difference in the serum concentrations within the therapeutic range achieved by the 18 and 20mg/kg infusions were noted (77% v 79% respectively). We have now utilised physiologically-based pharmacokinetic simulation software to assess the different loading doses of intravenous phenytoin.

Although the dearth of phenytoin pharmacokinetic data in children limits extensive validation of the model, the limited data available suggests that the model is appropriate.

There were, predictably, a greater number of data points below the 10 µg/mL level in the 18 mg/kg dose compared to 20 mg/kg. Again predictably, there were more data points above 20 µg/mL at the 20mg/kg dose. This increase was quantifiable using the model, with the 20mg/kg

dose increasing the mean C_{2h} by 1.9 µg/mL and AUC by 17 µg/mL/h. This increase in AUC may predispose to more adverse effects, although we note this is not supported by the only current study in this area [4]. Overall, the inter-individual variation in the phenytoin level achieved using either 18 or 20 mg/kg is greater than the increase noted with the increased dose.

These data are unable to predict the clinical significance of these differences, but do serve as a reminder to clinicians that the change in the loading dose of phenytoin may affect the clinical outcomes in some patients. Previous work in adult patients (16) has suggested that the minimum concentration of phenytoin in which clinical improvement is seen is 10 µg/mL. The reduction in the proportion of the population with sub-therapeutic concentrations (<10 µg/mL) from 22% to 15% achieved by increasing from 18mg/kg to 20mg/kg is therefore a potential benefit, decreasing the likelihood of unsuccessful treatment of status epilepticus. Conversely, the higher proportion of children with levels greater than 20 and 30 µg/mL with the 20mg/kg dose increases the risk of clinically significant toxicity, although we do note that there were very low rates of adverse effects in the 20mg/kg population of patients previously studied [4].

This work has also provided some insight into common clinical dilemmas that follow the use of a phenytoin infusion for the treatment of convulsive status epilepticus. The first of these is the timing and dose of maintenance therapy with phenytoin, should this be required. The current recommendation in the British National Formulary for Children (BNFc) for intravenous phenytoin maintenance doses are (for children up to 12 years) 2.5-5mg/kg BD (17). This has not been amended to take into account the increase in the recommended loading dose of phenytoin from 18 to 20mg/kg (18). The modelling data have indicated that the BNFc recommendation remains appropriate in that the commencement of maintenance dosing 12 hours following the loading dose and using both the 2.5mg and 5mg/kg doses, will maintain most children in the therapeutic reference range. However, the authors would recommend therapeutic drug monitoring in view of the narrow therapeutic index for phenytoin and the wide inter-individual variation in the pharmacokinetics of the drug.

The second most common clinical dilemma is to determine how best to increase the serum concentration in a child who has a sub-therapeutic phenytoin concentration (<10 µg/mL) following the initial loading dose. The model suggests that, assuming seizure control has been achieved, for a population with a blood level of less than 10 µg/mL, an increase in the first intravenous maintenance dose of 5 to 10mg/kg is likely to raise the blood level to within the

therapeutic reference range. A limitation of the modelling with respect to this analysis is that the low serum concentration may be attributable to patient factors (including concomitant medications), and that population-modelling may not necessarily accurately represent the change for an individual patient. We have also not been able to take account of confounders such as other anti-epileptic medication, or possible changes with age. Nevertheless, we consider that these data provide a starting point for future research, particularly in view of the fact there have been no previous attempts to model these data in children.

The use of modelling populations also has more generic limitations. We acknowledge that these data will not necessarily inform clinical practice for an individual patient. We also acknowledge that although the model fairly accurately predicted the mean C_{2h} for each dose, the number of sub-therapeutic levels for 20mg/kg was different to that observed in clinical work published previously (4). However, there have been many successful uses of modelling in paediatrics (12, 13), that have helped guide safe and effective prescribing practice. Clinicians need to be aware of the possibility of that a loading dose of 20mg/kg may cause high (supra-therapeutic) blood levels and therefore has the potential for greater toxicity (although only low rates have been reported to date).These data provide reassurance that both the currently-recommended BNFc iv loading dose for phenytoin (20mg/kg), as well as the iv maintenance dose recommendations, are appropriate.

Conclusions

Use of PBPK modelling suggests that children receiving the 20mg/kg intravenous loading dose are at slightly increased risk of supra-therapeutic blood levels. Therapeutic drug monitoring is required to monitor serum concentrations, and the dose regime suggested by the BNFc appears appropriate.

Figure Legends

Figure 1:

Simulated mean (solid line) and 95% confidence intervals (dashed line) of phenytoin systemic concentration vs time in 100 virtual children aged 2-10 years at doses of 18 mg/kg (red) and 20 mg/kg (green).

Figure 2:

(A) The concentration of phenytoin at 2 hours (C2h) post infusion at doses of 18 and 20 mg/kg. (B) The AUC of phenytoin at 0-12 hours post infusion at doses of 18 and 20 mg/kg. Both: Data show mean values, 95% confidence intervals and minimum and maximum values recorded within the simulation

Figure 3:

Mean plasma concentration of phenytoin dosed as 18mg/kg (red line) or 20mg/kg (green line) followed by a maintenance dose of 5 mg/kg given at 12 hours

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Competing Interests:

None to declare

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Figure

Figure 1

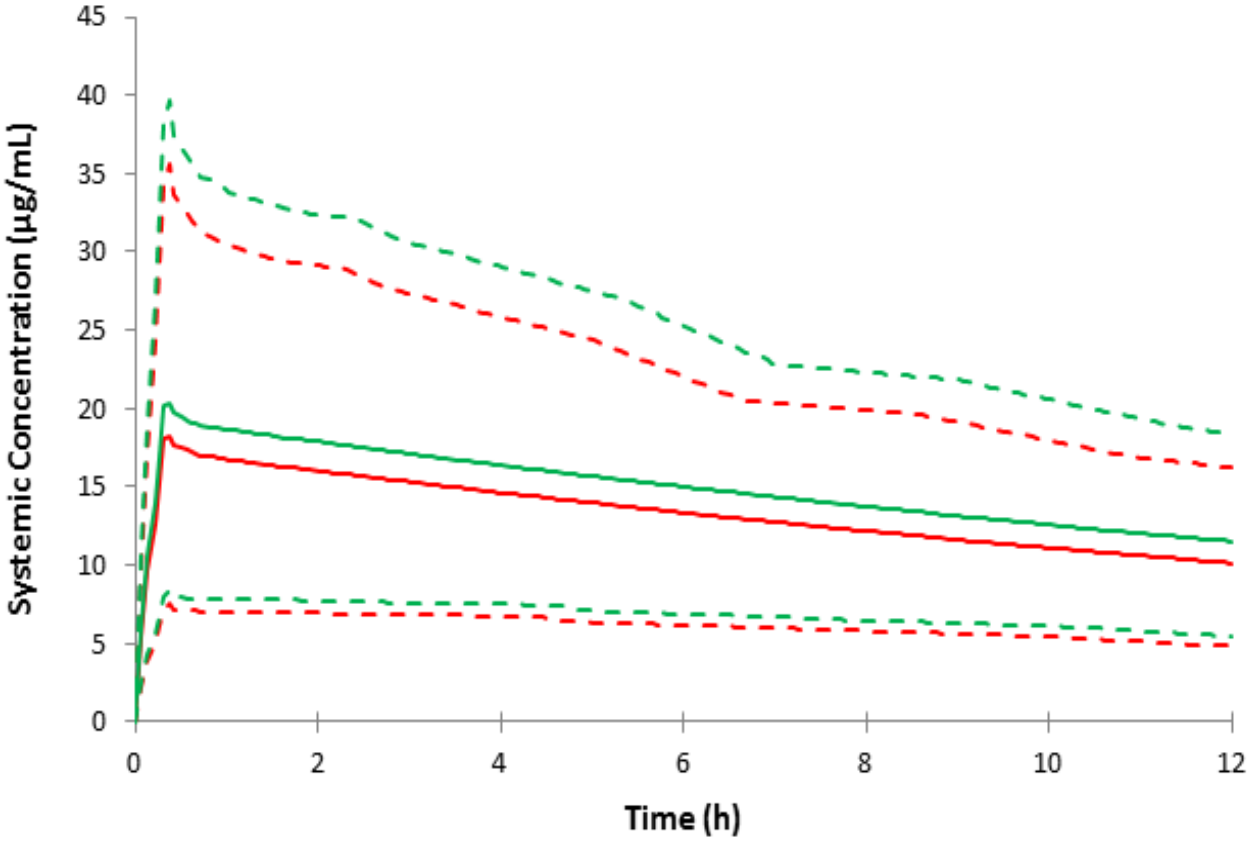
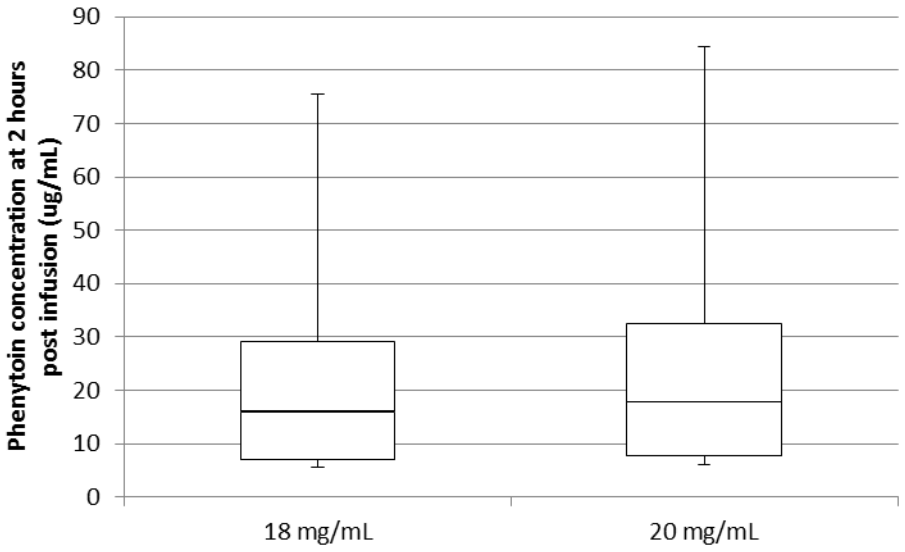


Figure 1

Simulated mean (solid line) and 95% confidence intervals (dashed line) of phenytoin systemic concentration vs time in 100 virtual children aged 2-10 years at doses of 18 mg/kg (red) and 20 mg/kg (green).

Figure 2

A


Phenytoin concentration at 2 hours post infusion (ug/mL)
90
80
70
60
50
40
30
20
10
0
18 mg/mL
20 mg/mL

B

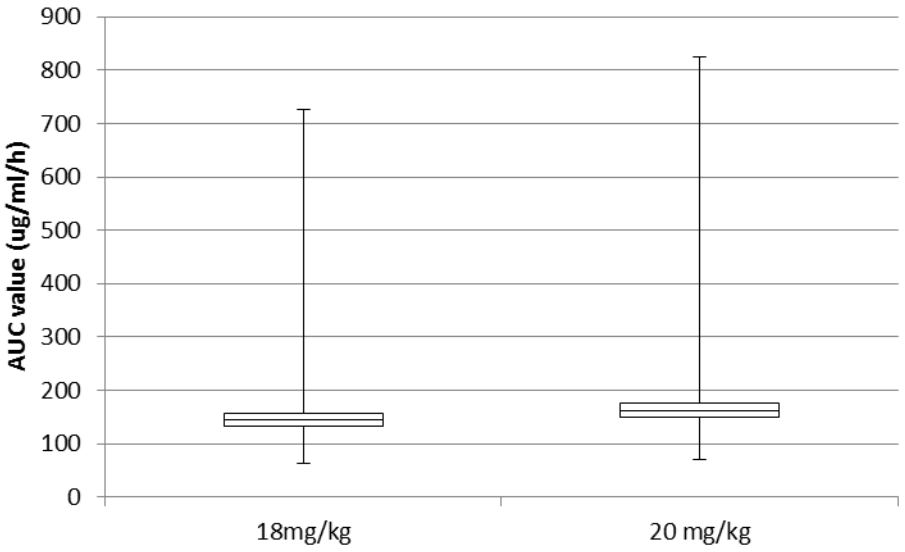

AUC value (ug/ml/h)
900
800
700
600
500
400
300
200
100
0
18mg/kg
20 mg/kg

Figure 2

(A) The concentration of phenytoin at 2 hours (C_{2h}) post infusion at doses of 18 and 20 mg/kg. (B) The AUC of phenytoin at 0-12 hours post infusion at doses of 18 and 20 mg/kg. Both: Data show mean values, 95% confidence intervals and minimum and maximum values recorded within the simulation

Figure 3

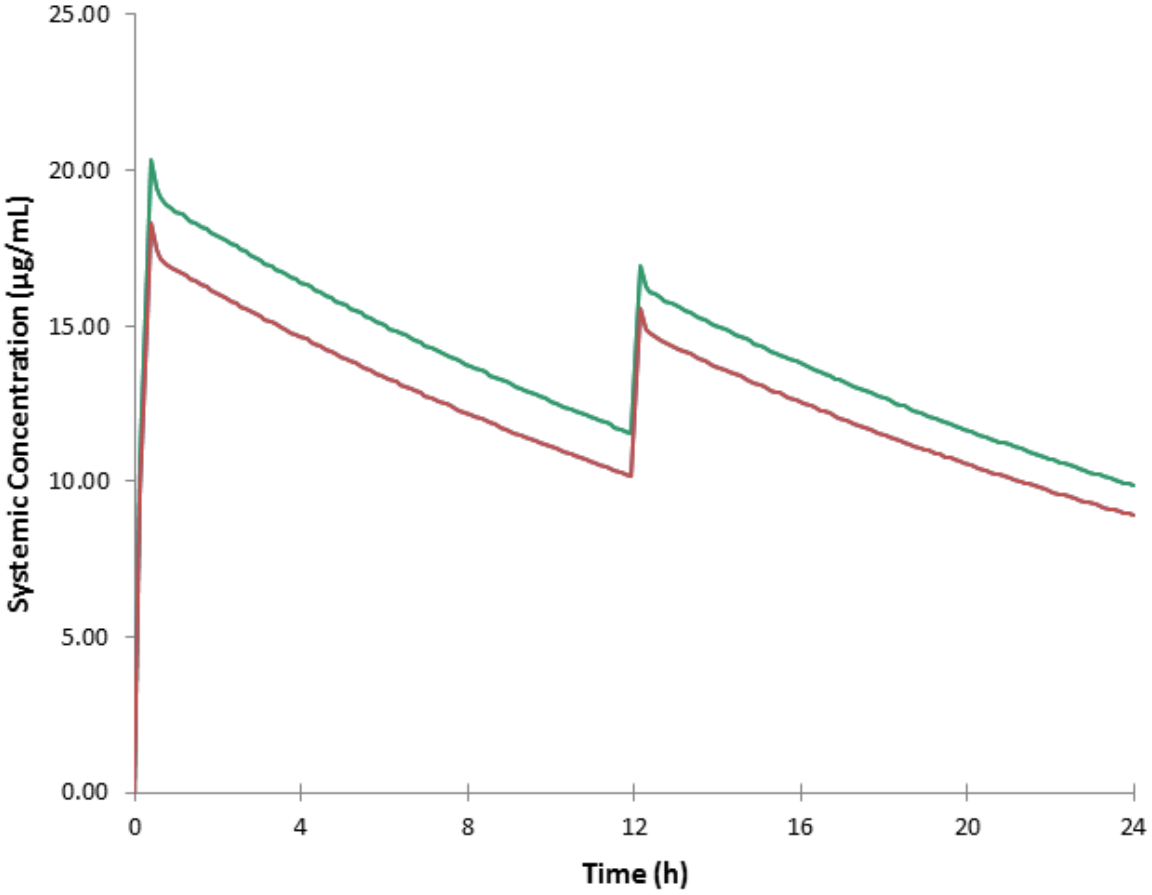

25.00
20.00
15.00
10.00
5.00
0.00
Systemic Concentration (µg/mL)
0
4
8
12
16
20
24
Time (h)

Figure 3

Mean plasma concentration of phenytoin dosed as 18mg/kg (red line) or 20mg/kg (green line) followed by a maintenance dose of 5 mg/kg given at 12 hours