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THERAPEUTIC HYPOTHERMIA DECREASES PHENYTOIN ELIMINATION IN CHILDREN WITH TRAUMATIC BRAIN INJURY

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Abstract

Objective—Preclinical and clinical studies have suggested that therapeutic hypothermia, while decreasing neurological injury, may also lead to drug toxicity that may limit its benefit. Cooling decreases cytochrome p450(CYP)-mediated drug metabolism and limited clinical data suggest that drug levels are elevated. Fosphenytoin is metabolized by CYP2C, has a narrow therapeutic range, and is a commonly used antiepileptic medication. The objective of the study was to evaluate the impact of therapeutic hypothermia on phenytoin levels and pharmacokinetics in children with severe TBI.

Design—Pharmacokinetic analysis of subjects participating in a multicenter randomized Phase III study of therapeutic hypothermia for severe TBI.

Setting—Intensive care unit at the Children’s Hospital of Pittsburgh

Patients—Nineteen children with severe TBI.

Interventions—None

Measurements and Main Results—A total of 121 total and 114 free phenytoin levels were evaluated retrospectively in 10 hypothermia- and 9 normothermia-treated children who were randomized to 48h of cooling to 32–33°C followed by slow rewarming or controlled normothermia. Drug dosing, body temperatures, and demographics were collected during cooling, rewarming, and post-treatment periods(8 days). A trend towards elevated free phenytoin levels in the hypothermia group(p=0.051) to a median of 2.2 mg/L during rewarming was observed and was not explained by dosing differences. Nonlinear mixed effects modeling incorporating both free and total levels demonstrated that therapeutic hypothermia specifically decreased the time-variant component of the maximum velocity of phenytoin metabolism(Vmax) 4.6-fold(11.6 to 2.53 mg/h) and reduced the overall Vmax by ~50%. Simulations showed that the increased risk for drug toxicity extends many days beyond the end of the cooling period.

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Conclusions—Therapeutic hypothermia significantly reduces phenytoin elimination in children with severe TBI leading to increased drug levels for an extended period of time after cooling. Pharmacokinetic interactions between hypothermia and medications should be considered when caring for children receiving this therapy.

Keywords

children; drug metabolism; hypothermia; phenytoin; pharmacokinetics; traumatic brain injury

INTRODUCTION

The clinical use of therapeutic hypothermia, defined as the controlled reduction of body temperature to 32–34°C, is expanding despite incomplete knowledge of its collateral effects on concomitant therapies. Randomized controlled trials(RCTs) documenting improvements in mortality and neurological outcomes following adult out-of-hospital cardiac arrest (1, 2) and hypoxic-ischemic encephalopathy(HIE) (3–6) have generated excitement surrounding the use of hypothermia for neuroprotection. In other cerebral ischemic injuries such as traumatic brain injury(TBI), however, consistent efficacy remains elusive. Clinical trials support the use of hypothermia to control elevated intracranial pressure(ICP), but multicenter RCTs have failed to demonstrate an improvement in mortality or neurological outcome (7–10). Adverse reactions such as increased hypotension requiring vasopressors and decreased cerebral perfusion pressure during the cooling and rewarming phases have been implicated as potential causes for the lack of benefit in these patients (10, 11). Additionally, it is well-known that guidelines-based therapy of TBI in children involves the use of a relatively large number of medications, contrasting treatment of HIE (12). It is unknown whether these hypothermia-related adverse events are directly due to cooling or due to medication-related interactions.

Therapeutic hypothermia is known to decrease cytochrome p450 (CYP) drug metabolism (13, 14), but clinical data remains sparse due to challenges in conducting pharmacokinetic studies in critically ill patients, especially children. Phenytoin and its prodrug fosphenytoin are metabolized by CYP2C9/19 and are commonly-used for seizure prophylaxis following TBI and in other populations receiving therapeutic hypothermia (15, 16). Independent of cooling, dosing is challenging and therapeutic monitoring is routinely performed due to its narrow therapeutic range and nonlinear Michaelis-Menton pharmacokinetics (metabolism does not increase proportionally with dose and is induced by injuries such as TBI) (17–20).

Based on the common use of phenytoin products in several populations treated with therapeutic hypothermia and limited available data, we aimed to determine the impact of therapeutic hypothermia on phenytoin levels and pharmacokinetics in children participating in a multicenter RCT. To achieve this goal, we developed a population pharmacokinetic model that simultaneously described free and total phenytoin concentrations as well as identified the covariates of phenytoin exposure after TBI. We further simulated the phenytoin concentration-time profiles in this population to best understand the risk and timing of phenytoin toxicity in children receiving therapeutic hypothermia to aid clinicians caring for similar patients.

PATIENTS AND METHODS

Patients

Children admitted to the University of Pittsburgh Medical Center with severe TBI who were enrolled in a prospective, Phase III RCT of therapeutic hypothermia and who received fosphenytoin or phenytoin were included in this study. The objective of the NIH-funded

Pediatric Traumatic Brain Injury Consortium: Hypothermia("Cool Kids Trial", clinicaltrials.gov:NCT00222742) was to determine the effect of induced, moderate hypothermia on outcomes after severe TBI in children. Inclusion criteria included age <18, a closed head injury, Glasgow Coma Scale(GCS) score <8(motor component <6). Exclusion criteria included the inability to initiate cooling within 6h of injury, a GCS of 3 and abnormal brainstem function, a normal initial CT scan, penetrating brain injury, unknown mechanism/time of injury, uncorrectable coagulopathy(PT/PTT >16/40 sec, INR >1.7), hypotension(systolic blood pressure less than the 5th percentile for age for >10 min), pregnancy, or a hypoxic episode(oxygen saturation <94% for >30 min). TBI management was protocol-driven as reported previously and in accordance with published pediatric guidelines (21, 22). All patients had external ventriculostomy drains and intraparenchymal catheters placed to monitor ICP and intracranial hypertension was treated using a tiered approach of positional maneuvers, continuous cerebrospinal fluid diversion, sedation, neuromuscular blockade, vasoactive medications, osmolar therapies(mannitol and/or hypertonic [3%] saline), and pentobarbital. Decompressive surgery was considered when medical therapies had failed. The study was approved by the local Institutional Review Board and informed consent was obtained.

Temperature management

Following hemodynamic and pulmonary stabilization, subjects were randomized to receive either controlled normothermia (36.5–37.9°C) or moderate hypothermia (32–33°C) for 48h. A rectal temperature probe was used to measure core body temperature. Target temperature attainment in those randomized to the hypothermia group was achieved using surface cooling (cooling blankets placed below the patient and ice packs placed in the groin and/or the axillae), cold intravenous saline (20–30mL/kg), and occasionally, gastric lavage as needed during cooling induction. Following 48h of cooling, patients were slowly re-warmed at a rate of 1°C per 12–24h until normothermia was attained. If intracranial pressure became elevated during rewarming, this rate was slowed to 1°C every 24–36h.

Drug administration, sampling, and data collection

Fosphenytoin is routinely used as prophylactic anti-seizure therapy in children following severe TBI at our institution. Within 12h of injury, an intravenous loading dose of 10–20mg/kg was administered to each patient and maintenance therapy of 5–7mg/kg divided every 12h was initiated 12h later. Blood samples for fosphenytoin therapeutic drug monitoring were drawn as part of routine clinical care. Dosing was in phenytoin-equivalents and adjusted based on clinical status and serum phenytoin levels in relationship to established therapeutic ranges (unbound/free phenytoin concentration[C_{free}], 1–2 mg/L); total phenytoin concentration[C_{total}], 10–20 mg/L) (23). Concentrations were measured at the Children's Hospital of University of Pittsburgh Medical Center using a particle-enhanced turbidimetric inhibition immunoassay(Beckman-Coulter, Brea, CA) with or without initial sample ultrafiltration, respectively. Clinical data collection occurred over 168h and included demographic information, injury severity scores(GCS and Injury Severity Score (ISS)), liver and renal function tests, hourly rectal temperatures, amount and timing of fosphenytoin or phenytoin doses, and any concurrent medications. All study times were measured from time of injury and all data were collected within a database by the University of Pittsburgh Data Coordinating Center.

Demographic data were expressed as mean ± standard deviation(SD) unless the data were not normally distributed, in which case median and range were reported. As an initial crude analysis, the potential effect of cooling on phenytoin C_{free} and cumulative drug dosing was explored by comparing group assignment (hypothermia or normothermia) on these measurements across the study periods using a two-way repeated-measures analysis of

variance with Graphpad Prism 5.04(Graphpad Software, La Jolla, CA). The analysis of C_{free} was limited to the rewarming and post-treatment periods to to focus on changes in drug elimination versus volume of distribution. If individual patients had multiple concentrations drawn within each period, they were first averaged so that each patient contributed equally to the group analysis.

Population pharmacokinetic analysis

To quantify and describe the specific impact of temperature on phenytoin pharmacokinetics, nonlinear mixed-effects modeling(NONMEM version VII, Icon Development Solutions, Hanover, Maryland) was also employed. This population-based approach can account for differences in drug administration timing and dosage that often occur as part of routine clinical care to determine population parameters (fixed effects) while preserving individual exposure (inter-subject variability – ISV) and residual variability (random effects) despite limited concentration sampling.

Free phenytoin disposition was initially based on a one-compartmental Michaelis-Menten pharmacokinetic model that was fit to the unbound concentration-time data:

$$\frac{\mathrm{dUnb}}{\mathrm{dt}} = -V_{\max} \times \frac{\mathrm{Unb}/V_1}{k_m + \mathrm{Unb}/V_1} \quad (1)$$

where V_{max} is the maximum velocity of metabolism(mg/h), k_m is the Michaelis-Menten rate constant(mg/L; at half of V_{max}), Unb is the amount of free phenytoin(mg), and V_1 is the volume of distribution(L). The total phenytoin was included in the model as follows:

$$\mathrm{Bou} = \theta_{\mathrm{prop}} \times \mathrm{Unb} \quad (2)$$

$$\mathrm{Total}_{\mathrm{drug}} = \mathrm{Unb} + \mathrm{Bou} \quad (3)$$

where Bou is the amount of bound phenytoin(mg) and θ_{prop} is the proportionality constant between the bound and unbound drug amounts. The total phenytoin($Total_{drug}$) is the sum of both Unb and Bou. As the fosphenytoin prodrug is very rapidly and completely converted to phenytoin and 100% bioequivalent following standard IV administration (24), conversion was not incorporated in the model.

Then, a second model (Figure 1) was fit, using the same one-compartmental Michaelis-Menten equation and the additional assumption that V_{max} varies as a function of time (V_{max} term in equation 1 replaced by $V_{max}(t)$ in Equation 4) as previous studies have demonstrated that TBI induces phenytoin metabolism.(18, 20)

$$V_{\max}(t) = V_{\max 0} + V \times (1 - e^{-k_{\mathrm{ind}} \times t}) \quad (4)$$

where $V_{max}(t)$ is the time-variant maximal velocity of metabolism, V_{max0} is the time-invariant maximum velocity of metabolism at baseline(mg/h), and V_{maxi} is the component of this velocity impacted by induction defined by the rate constant $k_{ind}(h^{-1})$ and time(h). Model selection and evaluation were completed based on visual inspection of goodness of fit plots, the objective function value provided by NONMEM, and the precision of the parameter estimates (see Supplemental Digital Content).

After base model selection and possible covariance between the random effects was identified, sex, age, weight, height, hypothermic group, and temperature were tested as

covariates on each pharmacokinetic parameter. A full model was then developed by combining the covariates individually identified as significant($p<0.001$) and refined by backward selection. This procedure and the nonparametric bootstrap analysis used to evaluate pharmacokinetic parameter estimate robustness and reliability is described in the Supplemental Digital Content.

Simulation

The population parameter estimates from the final model were used to simulate phenytoin elimination and C_{free}-time profiles of 1000 children receiving standard fosphenytoin dosing (20 mg/kg intravenous followed by 6 mg/kg/day divided every 12h) and either therapeutic hypothermia to 33°C or controlled normothermia. Population median and 90% confidence intervals of these concentrations and the percentage of simulated patients with supratherapeutic levels (above 2 mg/L) over time were determined. In order to avoid weight effects in the parameters, all individuals were simulated at 40kg.

RESULTS

Patient characteristics and temperature management

Nineteen children randomized to receive therapeutic hypothermia or normothermia were evaluated. Demographic information is provided in Table 1. The groups had similar sex, age, height, and weight. Although highly variable, the GCS and ISS suggest that injuries may have been worse in the hypothermia group. One patient in each group had the maximum ISS of 75 and the two additional subjects in the hypothermic group had GCS scores of 5 and 4 and ISS scores of 30 and 50, respectively. Barbiturates were administered more commonly in the normothermia (5 of 9 patients) versus hypothermia (3 of 10 patients) groups. No other medications known to interact with phenytoin were administered to any patient. Biomarkers of liver and renal function and serum albumin levels were similar among groups. The high upper ranges of liver enzymes in the normothermia group were driven by a single patient. Figure 2A shows the hourly patient rectal temperatures achieved through the cooling protocol. All patients attained goal temperatures within 10h of injury and were maintained within target ranges.

Effect of hypothermia on the phenytoin levels and dosing

There were 236 fosphenytoin and 17 phenytoin doses administered over the 168h study period. The majority of children received fosphenytoin exclusively; three patients received phenytoin loading doses and 2 patients received at least one maintenance dose of this medication. There were 121 phenytoin C_{total} and 114 C_{free} measured concurrently. Figure 2B shows there was a trend towards elevated phenytoin C_{free} in the hypothermia group during the rewarming and post-treatment periods (temp effect: p=0.051; study period effect: p=0.023; interaction: p=0.633). One patient in each group did not have levels drawn in one of the study periods and conservatively were excluded in 2-way repeated-measures ANOVA. Hypothermia children had a supratherapeutic median C_{free} of 2.2 mg/L during rewarming. Five of 9(56%) patients in this period and 6 of 10(60%) patients in the post-treatment period had levels greater than 2 mg/L. In the normothermic group, 3 of 8(38%) and 1 of 7(14%) patients had supratherapeutic levels, respectively. C_{total} followed similar trends (data not shown). Interestingly, Figure 2C demonstrates that the elevated concentrations were not explainable by higher dosing in the hypothermia group (temp effect: p=0.853; study period effect: p=0.249; interaction: p=0.660).

Population pharmacokinetic modeling

The time-variant Michaelis-Menten pharmacokinetic base model was significantly better at describing phenytoin C_{free} and C_{total} than the one-compartmental Michaelis-Menten model (objective function value reduction of 81.077 points, $p<0.01$) and was used for subsequent analyses. No covariance between the random effects identified was significant. Sex, age, and height did not affect any of the parameters. The weight effect on V_1 (equation 5) produced a large drop in the NONMEM objective function (44.23 points, $p<0.001$). The weight covariate also significantly explained part of the identified ISV on V_{max0} parameter (equation 6).

$$V_1=\left(\frac{\text{weight}}{40}\right)^{\gamma\text{wt1}} \times \theta_{V_1} \times \exp\left(\eta_{V_1}\right) \quad (5)$$

$$V_{\text{max0}}=\theta_{V_{\text{max0}}} \times \exp\left(\eta_{V_{\text{max0}}}+(\text{weight}-40) \times \text{wt}_2\right) \quad (6)$$

In Equations 5 and 6, θ and η terms are the fixed and random effect parameters, respectively; γ_{wt1} is the weight effect parameter on V_1; and wt_2 is the weight effect parameter on V_{max0}.

At this point, group assignment was not a significant covariate of any pharmacokinetic parameters. However, when temperature was incorporated as a continuous variable in the model (Equation 7), the improvement was significant ($p<0.01$).

$$V=\theta_V \times \exp\left(\eta_V+(\text{temp}-37) \times \text{temp}_1\right) \quad (7)$$

where $temp_1$ quantifies the temperature effect on V_{maxi} parameter. Table 2 lists the parameter estimates of the final population pharmacokinetic model with the corresponding relative standard error(RSE%). The goodness of fit plots for C_{free} and C_{total} (Figure E1, Supplemental Digital Content) indicate that the data were well described by the model. Data dynamics, as well as their dispersion, were well captured for both C_{free} and C_{total} by the model, although the 95th percentile was overpredicted (Figure E2, Supplemental Digital Content). The bootstrapping estimates (Table E1, Supplemental Digital Content) were very close to the final model parameter estimates.

Figure 3 shows the impact of covariates on the estimated pharmacokinetic parameters for each patient in the final time-variant model. The estimated V_1 and V_{max0} are both positively-correlated with patient weight and cooling reduces the estimated V_{maxi} values for patients in the normothermic and hypothermic groups. Importantly, therapeutic hypothermia led to a 4.6-fold (11.6 to 2.53mg/h) decrease in V_{maxi} at 33°C versus 37°C. The resulting impact on maximal velocity of metabolism (V_{max0}+V_{maxi}) is a reduction of 49.5%.

Simulation of temperature effects

The successful modeling provided an opportunity to simulate the magnitude and timing of therapeutic hypothermia's effect on phenytoin elimination, concentrations, and risk of toxicity. Forty-eight hours of 33°C hypothermia followed by slow rewarming reduced phenytoin elimination nearly 50% during the cooling and rewarming periods (Figure E3, Supplemental Digital Content) leading to elevated median C_{free} predominantly during the rewarming period (Figure 4). This effect of therapeutic hypothermia on phenytoin C_{free} persisted well beyond the end of the temperature management protocol. A greater proportion

of simulated children in the hypothermic group had a phenytoin C_{free} above the range commonly reported as a toxicity threshold (approximately 50% more patients had a level greater than 2mg/L).

DISCUSSION

We report that therapeutic hypothermia, as applied in the setting of a large RCT for pediatric TBI, significantly reduces phenytoin elimination. A trend towards elevated drug concentrations, particularly during rewarming, was observed in children randomized to hypothermia despite similar dosing as normothermic children. Population pharmacokinetic modeling demonstrated that therapeutic hypothermia decreased V_{maxi}; the parameter describing the time-dependent increase in phenytoin metabolism that occurs following TBI. Simulations predict that the increased risk for drug toxicity extends many days beyond the end of cooling. Unexpected medication dose-concentration relationships may have important implications in children receiving therapeutic hypothermia.

The non-linear mixed effects modeling fit the clinical data well and the pharmacokinetic parameter estimates obtained from the final time-variant model are consistent with published values. TBI is known to induce drug metabolism in adults 4–14 days after injury (25). Several clinical studies have similarly reported subtherapeutic phenytoin concentrations receiving standard dosing regimens or higher than expected phenytoin metabolism in TBI patients (18–20, 26). O'Mara et al. modeled C_{total} of 16 children and reported elevated phenytoin metabolism than previously established for children with epilepsy; K_m values were lower (meaning a greater enzyme affinity) and V_{max} values were higher (meaning greater enzyme capacity) (19, 27). Similarly, both McKindley et al. and Stowe et al. found Michaelis-Menton models that incorporated a time-variant V_{max} term best fit the majority of C_{free} in the ~10 adult and pediatric patients, respectively. In our study of 19 children, the V_{maxi} (estimate±SEM; 11.6±13.8 mg/h) was larger than the V_{max0} (6.73±1.53 mg/h) suggesting that the induced component of metabolism is an important contributor to the overall metabolism.

Cooling significantly decreased phenytoin elimination suggesting concentrations will be elevated clinically despite standard medication dosing. Small clinical and preclinical studies in adults have shown that levels of medications metabolized by CYP such as midazolam (28–30), fentanyl (31), and vecuronium (32) are elevated during cooling. In the only other pediatric RCT, Roka et al. showed that infants with HIE who were randomized to 33–34°C for 72h had a ~40% increase in morphine concentrations at the end of cooling and more often had a potentially toxic level (above 300 ng/mL) (33). The only pediatric clinical data involving phenytoin is from a single case report that reported V_{max} was decreased from 12.5 mg/h at 37.3°C to 1.2 mg/h at 33°C (34). In adults, Iida et al. administered phenytoin to 14 patients with brain injury and reported significantly higher concentration-time profiles during hypothermia and a 50% decreased phenytoin elimination rate (35). Unfortunately, without randomization, this study design was unable to separate temperature-related recovery of metabolic capacity with rewarming from a parallel, injury-related enzymatic induction. With the current RCT data, we report hypothermia to 32–33 °C decreased phenytoin V_{maxi} 4.6-fold and reduced the overall V_{max} after induction by ~50%, but did not affect K_m. This suggests that cooling specifically decreases overall phenytoin metabolic capacity by partially reversing the induction in metabolism that occurs in children with TBI. Our study was not designed to identify the mechanism driving this phenomenon, but possibilities include a direct effect on CYP2C9/19 and/or an interaction with injury processes leading to enzyme induction. Two recent reviews thoroughly detail the evidence for therapeutic hypothermia impacting drug pharmacokinetics through these processes (13, 36). Given the clinical data demonstrating an impact of cooling on metabolized drugs in HIE

patients (33) and healthy volunteers (29, 32) and established interactions between hypothermia and other disease processes that also impact drug metabolism such as cardiac arrest (30), it is likely that the current findings will be relevant to the clinical care of other hypothermia patients who receive phenytoin products.

The magnitude and timing of the altered pharmacokinetics resulting from therapeutic hypothermia is important clinically. With phenytoin, dose-concentration relationships are already very difficult to predict due to its narrow therapeutic range, nonlinear pharmacokinetics, and the abundance of clinical covariates in critically ill patients (37). We demonstrate that cooling children to 32–33°C for 48h with slow rewarming increased the proportion of children with supratherapeutic levels not during the cooling period, but during rewarming. Further, because of phenytoin's long half-life, the effect persisted at least 5 days beyond the end of the cooling period. This creates an extended time period of potentially unexpected drug responses after the active cooling period that may not be appreciated by clinicians. Intravenous phenytoin therapy is known to produce cardiac and neurological adverse drug reactions (38). Although hypotension and bradycardia are commonly attributed to rapid infusion of its propylene glycol diluent, bradydysrhythmias have also been reported with fosphenytoin (39). Whether medication adverse reactions impacts hypothermia-related outcomes in study populations where polypharmacy is common, such as TBI, is unknown, but warrants further investigation. The incorporation of pharmacokinetic endpoints and well-defined adverse reaction monitoring in future hypothermia RCTs would allow investigators to isolate the direct results of cooling versus its potential interactions with concurrent therapy (40).

The primary limitation of our study was its sample size. This precluded associations of levels with clinical endpoints and evaluations of the impact of additional covariates such as nutritional support, injury severity, and concomitant medications. The current study, however, is notable because it was conducted in the setting of a well-controlled RCT and is among the largest pharmacokinetic studies published in children. Traditional pharmacokinetic studies with intensive sampling of concentrations are often not feasible in critically-ill pediatric populations. Our approach was also innovative as it simultaneously fit the hundreds of C_{total} and C_{free} measured as part of routine clinical care using robust nonlinear mixed-effects modeling. We show that hypothermia significantly decreases phenytoin metabolism and identified time window of greatest concern. Results should be confirmed and correlated with relevant clinical parameters in larger populations and in children receiving cooling for other conditions such as in the recently proposed PharmaCool multicenter study (41).

CONCLUSIONS

We report therapeutic hypothermia significantly reduces phenytoin elimination in children with severe TBI leading to increased drug levels for an extended period of time after cooling. Regardless of efficacy of therapeutic hypothermia in the Cool Kids trial, children will continue to receive this treatment for a variety of disorders; therefore understanding the impact of therapeutic hypothermia on drug disposition is necessary to optimize its application and prevent drug toxicity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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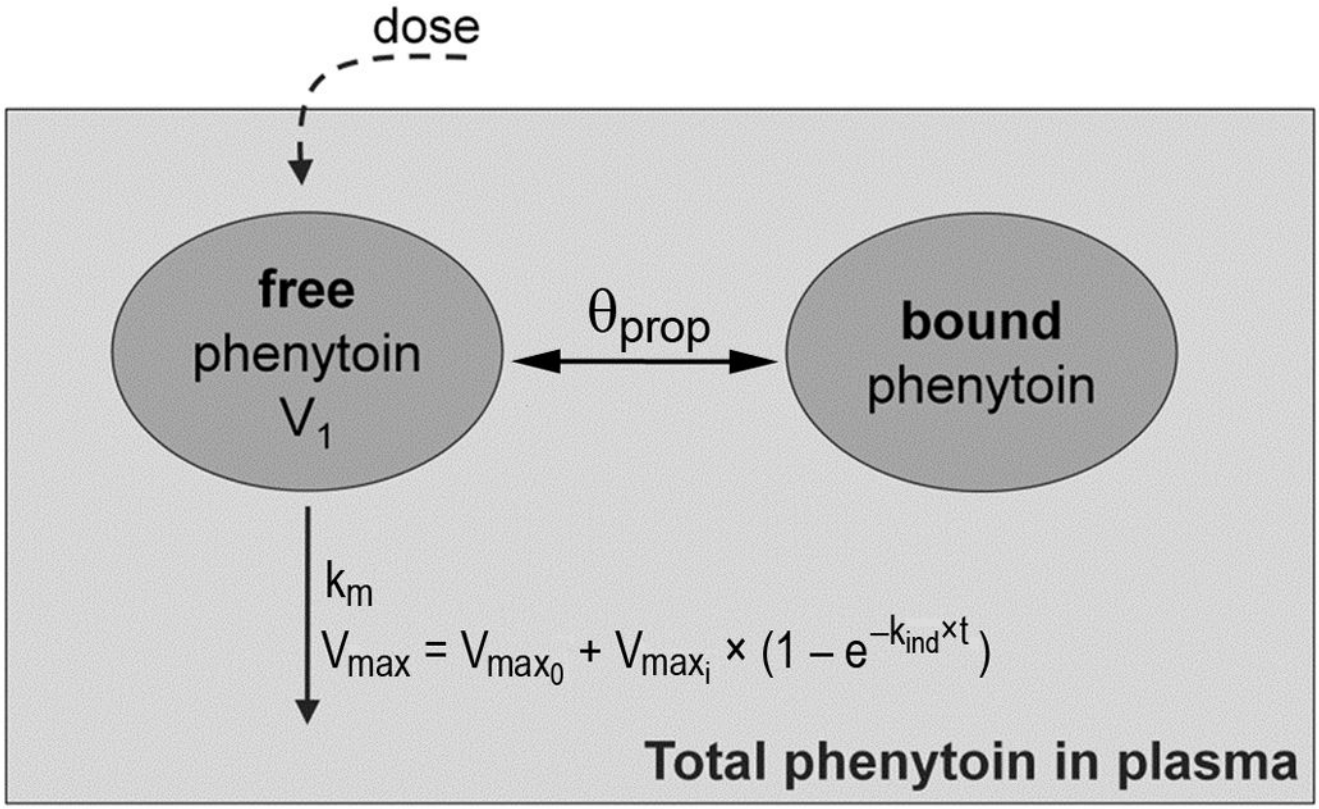

Figure 1. Schematic representation of the selected pharmacokinetic model

Two compartments represent the amount of free phenytoin (unbound) and of bound drug in plasma. V_1 is the volume of distribution, θ_{prop} is the proportionality constant between the bound and unbound drug amounts, k_m is the Michaelis-Menten elimination rate constant (mg/L), V_{max} is the maximum velocity of metabolism (mg/h), V_{max0} is the time-invariant maximum velocity of metabolism at baseline (mg/h), V_{maxi} is the time-dependent velocity defined by the rate constant k_{ind} (h^{-1}) and t is time (h). The total amount of phenytoin in plasma is the sum of unbound and bound phenytoin.

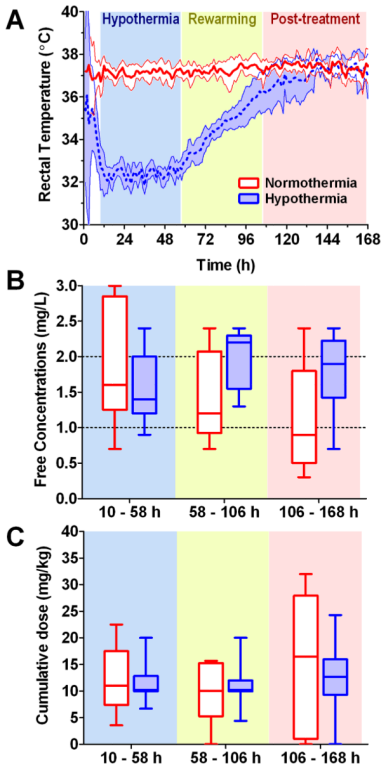

Figure 2. Patient temperatures, free phenytoin concentrations, and dosing

Protocol timing is organized into three shaded periods based on time from injury: hypothermia (or normothermia) from 10 – 58 h; rewarming (if in the hypothermia group) from 58 – 106 h; and post-treatment from 106 – 168 h. **A.** Hourly patient rectal temperatures demonstrate the success of the study protocol in achieving goal temperatures. Shaded regions are the 95% confidence intervals. **B.** There was a trend towards elevated free phenytoin concentrations in the hypothermia group in the rewarming and post-treatment periods (temp effect: p=0.051; study period effect: p=0.023; interaction: p=0.633). Dotted lines indicate the therapeutic range of 1– 2 mg/L. Box and whiskers graphs depict the mean, 95% confidence intervals, and range of each group. **C.** The cumulative dose of fosphenytoin administered to each patient was not different between the groups (temp effect: p=0.853; study period effect: p=0.249; interaction: p=0.660).

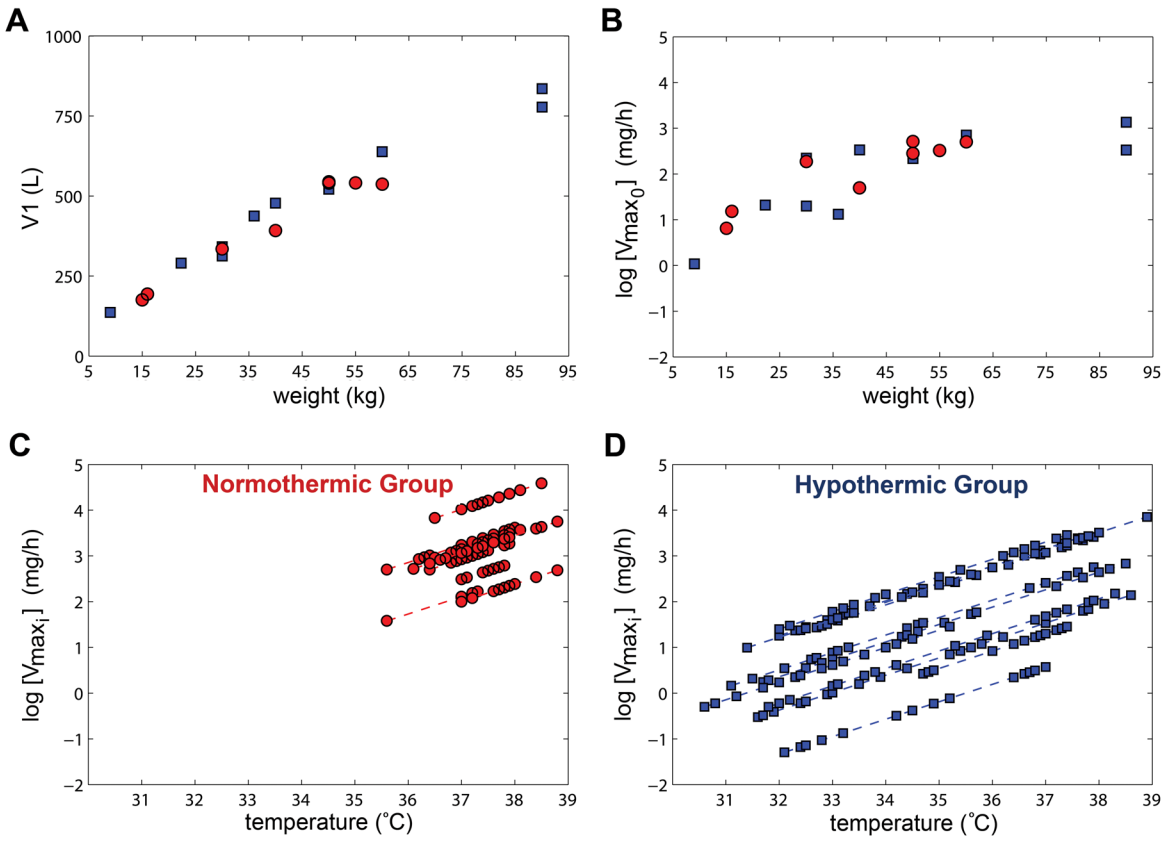

Figure 3. Impact of covariates on the estimated pharmacokinetic parameters

Circles(red) and squares(blue) are patients in the normothermic and hypothermic groups, respectively. **A/B.** Estimates of volume distribution (V_1) and time-invariant maximum velocity of metabolism at baseline (V_{max0}) for each patient is positively-correlated with weight. **C/D.** Estimated time-dependent velocity of metabolism (V_{maxi}) on the log scale is reduced with lower temperatures for the normothermic and hypothermic patients versus temperature.

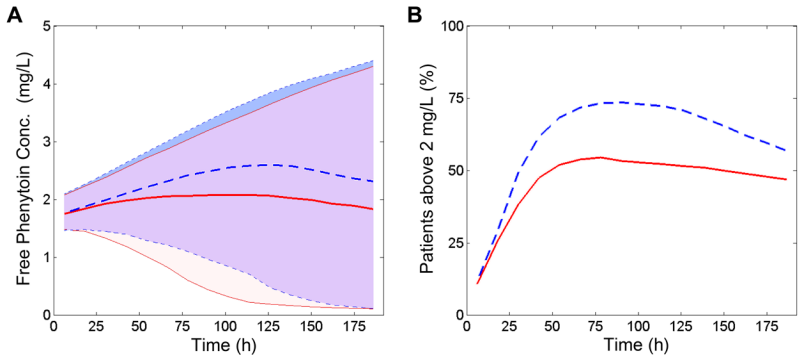

Figure 4. The magnitude and timing of the effects of temperature on free phenytoin concentrations

Simulations of 1000 children receiving either therapeutic hypothermia or controlled normothermia. Solid lines/lightest(red) shading represents the normothermic group while dashed lines/darkest(blue) shading represents the hypothermic group. The simulated fosphenytoin dosing schedule was 20 mg/kg IV loading dose followed by 6 mg/kg/day divided every 12 h. The cooling protocol involved hypothermia induction over 6 h to 33 °C, hold at 33 °C for 48 h, and then slow rewarming (1 °C per 24 h) to 37 °C (depicted in Figure E3, Supplemental Digital Content). Controlled normothermia patients were fixed at 37 °C. All individuals were simulated with a weight of 40 kg. **A.** Unbound phenytoin concentrations are elevated in patients receiving hypothermia versus normothermia as shown by the population predicted median (lines) and 90% confidence interval (shading) over time. **B.** Percentage of simulated children with free phenytoin concentrations above the 2 mg/L toxicity threshold in each group versus time.

Table 1

Demographics

	Normothermia (n = 9)	Hypothermia (n = 10)
Male - n (%)	6 (67%)	5 (50%)
Height (cm) - mean (SD)	142 (29)	144 (31)
Weight (kg) - mean (SD)	39 (16)	47 (27)
Age (yr) - median (range)	13.6 (2.5–16.2)	11.1 (2.1–14.7)
GCS - median (range)	7 (3–7)	5 (3–8)
ISS - median (range)	21 (16–75)	33.5 (25–75)
Albumin		
Day 1 - mean (SD)	3.2 (0.7)	3.0 (0.5)
Day 3 - mean (SD)	2.4 (0.5)	2.4 (0.2)
Day 7 - mean (SD)	2.2 (0.3)	2.7 (0.4)
AST - median (range)	60 (38–1303)	41 (31–111)
ALT - median (range)	26 (11–530)	30 (23–88)
ALP - median (range)	145 (70–382)	168 (66–288)
T. bili - mean (SD)	0.7 (0.8)	0.6 (0.4)
Serum creatinine - mean (SD)	0.5 (0.2)	0.5 (0.2)

Measurements are from the day of admission unless otherwise noted. AST = Aspartate transaminase, ALT = Alanine transaminase, ALP = Alkaline phosphatase, and T. bili = total bilirubin.

Table 2

Population pharmacokinetic parameter estimates

Parameter	Estimate (RSE%)	ISV (RSE%)
V_1 (L) = (weight/40)$^{\gamma_{wt1}}\times\theta_{V1}$	γ_{wt1} = 0.809 (9.28) θ_{V1} = 433 (3.57)	10.1 (50.4)
V_{max0} (mg/h) = $\theta_{Vmax0}\times exp$[(weight-40)×wt_2]	θ_{Vmax0} = 6.73 (22.8) wt_2 = 0.0298 (33.6)	55.0 (47.1)
V_{maxi} (mg/h) = $\theta_{Vmaxi}\times exp$[(temp-37)×$temp_1$]	θ_{Vmaxi} = 11.6 (119) $temp_1$ = 0.381 (51.5)	110 (88.2)
k_m (mg/L)	0.483 (53.37)	
θ_{prop} (unitless)	8.15 (3.9)	15.2 (51.3)
k_{ind} (h^{-1})	0.00426 (97.2)	
Log residual error C_{free} (mg/L)	0.0372 (47.6)	
Log residual error C_{total} (mg/L)	0.0144 (20.0)	

Model pharmacokinetic estimates, equations describing their relationships with covariates, and their corresponding relative standard error (RSE %) from the final full model. ISV = inter-subject variability expressed as coefficient of variation (%); θ terms are the fixed effect parameters, V_1 = apparent volume of distribution; γ_{wt1} = weight effect parameter on V_1; V_{max0} = time-invariant maximum velocity of metabolism at baseline; wt_2 = weight effect parameter on V_{max0}; V_{maxi} = time-dependent velocity defined by the rate constant k_{ind} and time t; $temp_1$ = temperature effect parameter on V_{maxi}; k_m = Michaelis-Menten elimination rate constant; θ_{prop} = proportionality constant for the bound phenytoin; k_{ind} = rate constant for induction of metabolism. The phenytoin fraction unbound (reciprocal of θ_{prop}) was 0.123±0.005.