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Theophylline Population Pharmacokinetics and Dosing in Children Following Congenital Heart Surgery with Cardiopulmonary Bypass

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Abstract

Children undergoing cardiac surgery requiring cardiopulmonary bypass (CPB) frequently develop acute kidney injury due to renal ischemia. Theophylline, which improves renal perfusion via adenosine receptor inhibition, is a potential targeted therapy. However, children undergoing cardiac surgery and CPB commonly have alterations in drug pharmacokinetics. To help understand optimal aminophylline (salt formulation of theophylline) dosing strategies in this population, a population-based pharmacokinetic model was developed using nonlinear mixed-effects modeling (NONMEM) from 71 children (median age: 5 months [90% range: 1 week – 10 years]) who underwent cardiac surgery requiring CPB and received aminophylline as part of a previous randomized controlled trial. A one-compartment model with linear elimination adequately described the pharmacokinetics of theophylline. Weight scaled via allometry was a significant predictor of clearance and volume. In addition, allometric scaled clearance increased with age implemented as a power maturation function. Compared to prior reports in non-cardiac children, theophylline clearance was markedly reduced across age. Applying the final population pharmacokinetic model, optimized empiric dosing regimens were developed via Monte Carlo simulations. Doses 50-75% lower than those recommended in non-cardiac children were needed to achieve target serum concentrations of 5-10 mg/L.

Keywords

Pediatric; Aminophylline; Pharmacokinetics; Acute Kidney Injury; Congenital Heart Defect; Population Pharmacokinetics; Cardiopulmonary Bypass

INTRODUCTION

Renal ischemia in the setting of sepsis or organ failure (e.g. cardiac disease, respiratory distress, liver failure) is one of the common causes of acute kidney injury (AKI) in critically ill infants and children.^(1,2) Children undergoing cardiac surgery requiring cardiopulmonary

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Conflict of Interest

The authors have no conflict of interest, real or perceived, to report.

bypass (CPB) are particularly susceptible to ischemic events with rates of AKI as high as 25-50%.(3–7) In addition, AKI is an independent predictor of morbidity and mortality in critically ill children(8–10) and a risk factor for the development of chronic kidney disease.(11) Despite the high incidence and clinical impact of AKI in children after cardiac surgery requiring CPB, therapeutic approaches to help prevent or treat AKI are lacking.

While the development of AKI is likely multifactorial, a primary renal vasoconstrictive event with decreased kidney perfusion and subsequent parenchymal ischemia is critical in its pathogenesis and development.(12) Animal models have demonstrated that vasoconstriction after hypoxemia-induced renal dysfunction in newborns is largely adenosine-mediated.(13) An adenosine receptor antagonist such as theophylline (often given as its salt form aminophylline for intravenous dosing), therefore, may limit renal afferent arteriole vasoconstriction after ischemic kidney injury and improve renal perfusion and glomerular filtration rate (GFR). Randomized placebo-controlled trials have already demonstrated that prophylactic aminophylline reduces the incidence of severe renal dysfunction in asphyxiated newborns.(14–16) In a recent retrospective analysis of critically ill children with AKI, aminophylline therapy was associated with improvement in GFR.(17) A similar benefit from aminophylline may also be suggested in children undergoing cardiac surgery requiring CPB in whom ischemic kidney injury is common.

To develop aminophylline as a potential targeted therapeutic approach for AKI in children undergoing cardiac surgery with CPB, understanding the pharmacokinetics and dose requirements in this population is critical. The pharmacokinetics of theophylline have been previously described in preterm and term neonates when used for the treatment of apnea(18–22) and in children for asthma.(23,24) However, the pharmacokinetics in infants and children undergoing cardiac surgery with CPB have not been reported. Cardiac disease, surgery, and CPB can all impact drug pharmacokinetics.(25–27) In addition, optimizing theophylline exposure is important as theophylline has a narrow therapeutic index and toxicities including cardiac arrhythmias and seizures can be seen at higher exposures (i.e. concentrations >20 mg/L).(28) The objectives of the current study were 1) to evaluate the pharmacokinetics of theophylline in children after cardiac surgery requiring CPB using a population-based approach and 2) to identify an empiric aminophylline dosing strategy that optimizes achievement of target serum drug concentrations.

METHODS

General Study Design

This was a pharmacokinetic analysis of data collected as part of a randomized double-blinded, placebo-controlled study which examined whether post-operative administration of aminophylline reduced the incidence of AKI in children with congenital heart defects undergoing CPB and cardiac surgery (clinicaltrials.gov identifier NCT01245595).(29) The original study was performed at a single tertiary care center (Lucile Packard Children's Hospital Stanford) and was approved by the Stanford University Institutional Review Board. Informed consent and assent where applicable were obtained for all patients. To be eligible for the study patients were required to be <18 years of age with a congenital heart defect undergoing cardiac surgery with CPB. Exclusion criteria included: < 36 weeks corrected

gestational age at the time of surgery; pre-operative continuous renal replacement therapy (CRRT); post-operative extracorporeal membrane oxygenation (ECMO); history of tachyarrhythmias, seizures, aspartate aminotransferase or alanine aminotransferase > 3 times upper limit of normal, coagulopathy (INR > 1.5 while not taking warfarin), sepsis, fever (>102° F), or hypothyroidism.

For the population pharmacokinetic analysis, only patients randomized to receive aminophylline were analyzed. Following cardiac surgery with CPB, these patients were administered aminophylline in the cardiovascular intensive care unit (CVICU). Aminophylline was given as a loading dose of 5 mg/kg (4 mg/kg theophylline equivalent) intravenous (IV) over 30 minutes followed by 1.8 mg/kg (1.4 mg/kg theophylline equivalent) IV every six hours for 72 hours (total 13 doses). Measurement of daily theophylline trough serum concentrations (i.e. 5 to 6 hours after the last dose) was scheduled, and the dose was adjusted by an unblinded study pharmacist based on a standardized sliding scale to achieve a theophylline trough serum concentration of 5-10 mg/L. Quantitative determination of theophylline serum concentrations were performed by the Stanford Clinical Laboratory using a particle enhanced turbidimetric inhibition immunoassay, PETINIA (Dimension clinical chemistry system, Siemens Healthcare Diagnostics Inc., Newark, DE). The lower limit of quantification was 0.2 mg/L. The within-run and total coefficient of variation for the assay were less than 5%.

Population Pharmacokinetic Analysis

A population pharmacokinetic model was developed from the theophylline serum concentration time data using the nonlinear mixed-effects modeling program NONMEM (Version 7.2, Icon Development Solutions, Ellicott City, MD). Aminophylline dose was converted to theophylline equivalents by multiplying by 0.79. The first order conditional estimation method with interaction was used throughout the model building and evaluation process. A one-compartment pharmacokinetic model with first-order elimination was implemented. Inter-individual variability was evaluated on clearance (CL) and volume of distribution (V) using an exponential error model. To model the residual variability (i.e. intra-individual or “measurement error” that captures the difference between the model predicted concentration for an individual and the observed concentration in that individual) both additive and proportional error models were evaluated. Selection between models was based on the difference in the NONMEM objective function value (OFV), visual comparison of standard diagnostic plots, and model plausibility and stability. The difference in OFV between two models has an approximate χ^2 distribution with degrees of freedom equal to the difference in the number of parameters between models. Significance was set at a decrease in OFV larger than 10.83, corresponding to a $p < 0.001$.

Once the structural pharmacokinetic model was established, biologically and/or clinically plausible covariates were evaluated for their influence on pharmacokinetic parameters. Based on previous population pharmacokinetic modeling for a range of compounds in neonates and children, the effect of weight on CL and V was implemented *a priori* using an allometric model with the exponent defining the relationship fixed to 0.75 and 1, respectively.(30) Weight was measured pre-operatively on admission. After adding weight to

the model, the effect of maturational changes on CL was explored using patient's age as a predictor using power, exponential, and sigmoid $E_{\max}$ maturation functions.(31)

Due to the potential for maturational delay of the cytochrome P450 isoforms (i.e. CYP1A2) important in theophylline metabolism in infants and young children, renal excretion of unchanged theophylline may have been an important route of elimination.(28) Biomarkers of kidney function were evaluated as predictors of CL and include daily estimated glomerular filtration rate (eGFR), daily urine output (in ml/kg/h), and diagnosis of AKI. eGFR was calculated using the 'original' Schwartz formula.(32) AKI was defined by the Kidney Diseases: Improving Global Outcomes (KDIGO) AKI criteria using serum creatinine criteria.(33) Cardiac disease severity, surgical procedure complexity and post-operative cardiac function were also examined as covariates on CL using the Risk Adjustment in Cardiac Surgery(34) (RACHS-1; categories 1-6 category), CPB time, and Vasoactive Inotropic Score (VIS). The VIS is a composite index of concomitant inotropic drugs (dopamine, dobutamine, epinephrine, norepinephrine, milrinone and vasopressin) based on dose.(35) Scores can range from 0 to >25 and were calculated daily. Biomarkers of liver injury (i.e. alanine aminotransferase) were not available for covariate analysis. However, the potential for resolving liver injury following CPB to impact clearance was evaluated by examining post-operative day as a covariate on clearance. Lastly, bioelectrical impedance was evaluated as a predictor of volume. Bioelectrical impedance is a noninvasive measure of total body water previously used in cardiac surgical patients (36,37) that was measured daily (RJL Systems, Clinton Township, MI). The effect of a continuous covariate on a parameter was modeled using a power function. Continuous covariates were scaled to their median values. Categorical covariates were modeled proportionally, i.e. the fractional change in clearance when the categorical covariate was true. Covariates that were measured daily during the theophylline treatment period (e.g. eGFR, VIS, bioelectrical impedance, and urine output) were allowed to vary with time in the model.

After first incorporating the allometric model of weight on CL and V, the covariate model was built using a standard forward addition backward deletion procedure. Covariates were added in a stepwise manner to the model in the order of their reduction in the OFV. During forward stepwise addition, a covariate was allowed to enter the model as long as the decrease in OFV due to its addition was larger than 3.84, corresponding to a $p < 0.05$. After the stepwise addition terminates, the model is pruned using backward elimination. Covariates were eliminated one at a time, until the removal of a covariate results in an OFV increase of more than 10.83, corresponding to a $p < 0.001$.

To evaluate the accuracy and stability of the final pharmacokinetic model, a non-parametric bootstrap re-sampling method was performed using the NONMEM support software Perl-speaks-NONMEM (PsN, Version 3.6.2). A total of 1000 bootstrap datasets were generated from the original data set by repeated sampling with replacement, and the final pharmacokinetic model was used to estimate model parameters for each data set. In addition, the final pharmacokinetic model was assessed using an internal evaluation procedure by computing the normalized prediction distribution errors (NPDE) of 5000 simulated datasets compared to the observed dataset.(38,39)

Dose-Exposure Relationships

Monte Carlo simulations were conducted to optimize aminophylline dosing regimens in children with congenital heart defects undergoing CPB and cardiac surgery. Using the final population pharmacokinetic model parameters estimates, the pharmacokinetic profiles of 1,000 'hypothetical' children were repeatedly simulated. Children aged 1 month, 6 months, 1 year, 2 years, 6 years, and 10 years were evaluated. Weight for children was implemented using age-specific distributions from growth charts from the World Health Organization (<2 years) and Center for Disease Control (≥ 2 years).^(40,41) Loading doses were examined ranging from 2 to 8 mg/kg given intravenous over 30 minutes. 'Maintenance' doses given as an intermittent dose every 6 h or as a continuous infusion were assessed (daily doses 2 to 10 mg/kg/day). The predicted peak serum concentration one hour after the loading dose and predicted trough serum concentration at steady-state with maintenance dosing were examined. A trough serum concentration between 5 – 10 mg/L was targeted based on prior reports that have used aminophylline to improve renal dysfunction in critically ill children.^(17,42) The loading dose and maintenance dose that maximized the probability of achieving the target trough serum concentration for each age were selected. In addition, the frequency of serum concentrations considered potentially toxic (i.e. > 20 mg/L) were also examined.⁽²⁸⁾

RESULTS

Patients

A total of 71 children randomized to aminophylline postoperatively following cardiac surgery with CPB had theophylline concentrations available for analysis. Patient characteristics are presented in Table 1. Twelve patients were <1 month of age, 37 patients were 1 month to 1 year of age, 19 patients were 1 to 12 years of age, and 3 patients were 13 to 18 years of age. AKI was diagnosed in 40 patients (22 patients with stage 2 or 3) post-operatively. The median vasoactive inotropic score (VIS) in the first 24 hours post-operative was 8 (90% range 0 – 15). The median bioelectrical impedance on the first post-operative day was 408 ohms (90% range 245 – 588 ohms).

Of the 71 children, 55 (77%) received a full treatment course of aminophylline. Aminophylline was discontinued early for the following reasons: catheters removed preventing blood sampling (n=8), clinical team decided to remove patient from the study (n=5), physician decision to initiate aminophylline outside of the study protocol (n=2), and cardiopulmonary arrest (n=1).

In total, 194 theophylline serum concentrations were available for PK analysis with 58 patients (82%) having 3 measured serum concentrations. Most serum concentrations (n=174; 90%) were measured 5 to 6 hours after the last dose. None were below the lower limit of quantification. Thirteen neonates had a theophylline serum concentration > 10 mg/L at some point during the treatment course; 10/13 (77%) were less than 6 months old. In the 59 patients with a theophylline serum concentration on postoperative day 3 (final day of aminophylline), the median concentration was 7.8 mg/L (90% interval 4.2 – 11.8 mg/L). The corresponding median dose on postoperative day 3 was 1.8 mg/kg (90% interval 1.2 – 2.6

mg/kg) every 6 h with 48/59 (81%) having required at least one dose adjustment by the study pharmacist.

Population Pharmacokinetic Analysis

Theophylline serum concentrations were adequately described by a one-compartment model with first-order elimination and an exponential error model for interindividual variability on CL and V. The residual variability (or intra-individual variability) was best described by a proportional error model. The addition of pre-operative weight scaled via allometry to predict CL and V significantly improved the model fit (OFV -117; $p < 0.001$). After incorporating the allometric model of weight on CL and V, a power maturation function of age was identified as a significant predictor of CL (OFV -50; $p < 0.001$; **Figure 1**). An exponential maturation function of age was also identified as a significant predictor of CL (OFV -16; $p < 0.001$), but the reduction in OFV was not as great as with the power function. Implementation of a sigmoid $E_{\max}$ maturation function of age did not improve the model fit compared to the power function, and model parameters were unidentifiable. Therefore, a power maturation function of age was selected for inclusion in the model. VIS was also found to significantly impact theophylline CL during forward stepwise addition of the covariate model (OFV -4; $p < 0.05$). No other covariates examined during forward addition significantly impacted theophylline CL or V. During backward elimination, VIS did not meet statistical criteria for remaining in the model and was removed.

The final population pharmacokinetic model parameter estimates are presented in **Table 2**. The population predicted CL and V for a patient were:

$$CL_{(L/h)} = 0.13 \times \left(\frac{Weight}{5.8 \text{ kg}} \right)^{0.75} \times \left(\frac{Age}{0.4 \text{ year}} \right)^{0.22}$$

$$V_{(L)} = 2.96 \times \left(\frac{Weight}{5.8 \text{ kg}} \right)$$

In general, observed versus population predicted concentrations showed no systemic bias, and the weighted residuals were homogeneously scattered (**Figure 2**). The parameter estimates as found by bootstrap were in agreement with those obtained by the final population pharmacokinetic model (**Table 2**), indicating reliability of the final model estimates. Internal model evaluation also demonstrated that the final model performed well in describing the observed data. The mean NPDE was 0.05 (theoretical mean is zero) with a variance 1.0 (theoretical variance is 1.0), and 90.2% of observations fell inside the theoretical 90% prediction interval. In addition, there were no major trends in NPDE across time after dose, weight, or age (**Figure 3**). However, in the older age and higher weight patients, a slight trend toward under-prediction of serum concentrations may be present but is difficult to assess given the limited data.

Dose-Exposure Relationships

Optimized loading and maintenance doses of aminophylline were calculated at each age using Monte Carlo simulations and a target serum concentration of 5 – 10 mg/L. A loading dose of 5.0 mg/kg given over 30 minutes was appropriate across all ages. This dose resulted in a median serum concentration one hour after start of the infusion of 7.4 mg/L (90% range

4.6 – 11.0 mg/L) with 80% of simulated patients achieving the target serum concentration. No simulated patients had a peak serum concentration >20 mg/L. Optimized maintenance doses given intermittently every 6 hours or as a continuous infusion are shown in **Table 3**. The optimized dose in mg/kg decreased with decreasing age. For example, children < 1 year required 30-40% lower doses in mg/kg than children 6 years of age to achieve similar target trough exposure. Variability in exposure for a given age was observed, and up to 40% of children were predicted to not achieve the target trough exposure with the optimized maintenance dose. However, trough serum concentrations > 20 mg/L at steady-state were infrequent at the optimized maintenance dosing (0.5% for all ages). In addition, when aminophylline was given as intermittent dosing every 6 h, predicted peak serum concentrations >20 mg/L were also infrequent at steady-state (1.4% for all ages).

DISCUSSION

The current study describes the first report of the pharmacokinetics of theophylline in children after cardiac surgery requiring CPB. Similar to previous population pharmacokinetic models in non-cardiac infants and children,(20,21,23) theophylline pharmacokinetics were adequately described by a one-compartment model with linear elimination. However, theophylline clearance allometrically scaled by weight was 50-75% lower in children after cardiac surgery requiring CPB compared to reports in children without cardiac disease (ages ranging from 1 month to 16 years).(23,24,28,43) The volume estimate of 0.51 L/kg in the current study was similar to reports in children without cardiac disease.

Limited pediatric pharmacokinetic data are available to help guide drug dosing decisions in children undergoing cardiac surgery requiring CPB. Extrapolation of general pharmacologic understanding from children without cardiac disease can be a useful starting reference. For example, the pharmacokinetics of theophylline in non-cardiac children (and adults) is known to be highly variable(28), and it is reasonable to assume that large variation in theophylline pharmacokinetics will be present in children undergoing cardiac surgery requiring CPB. However, extrapolation of dose strategies from non-cardiac children may be misguided, especially for theophylline which has a narrow therapeutic window.(28) Therefore, a detailed examination of theophylline pharmacokinetics in children who had cardiac surgery requiring CPB is critical to help understand optimal dosing strategies of aminophylline in this population.

Size, maturation, altered physiology, concomitant medications, and intraoperative procedures such as CPB may all impact drug pharmacokinetics in the post-operative period, and each were explored in the current study as potential covariates on theophylline pharmacokinetics. Weight was identified to be a significant predictor of both clearance and volume. Body size is a well-known scalar of clearance and volume in children(30) and has been previously described as a predictor of clearance and volume for theophylline in non-cardiac children.(20,21) After accounting for size, a power maturation function of age adequately characterized the maturational changes in theophylline clearance. Age as a predictor of theophylline clearance has also been described in non-cardiac children. (20,21,23) The increase in clearance (L/h/70kg) with age most likely represents CYP1A2

ontogeny as this is the major liver enzyme responsible for theophylline metabolism.(28) Biomarkers of liver injury (i.e. alanine aminotransferase) may have been helpful in identifying those with impaired liver metabolism, but these were not available for analysis. In place of biomarkers of liver injury, surrogates of potential liver injury such as CPB time and level of inotropic support were used and not found to impact clearance. In those with reduced liver metabolism due to immaturity or injury, renal elimination of unchanged theophylline may become clinically relevant,(28) however renal function as measured by GFR did not impact theophylline clearance. No other significant predictors of theophylline clearance or volume were identified.

Compared to prior reports in non-cardiac children,(23,24,28,43) theophylline clearance was lower for all ages studied. For example, the predicted clearance in a 6 month old after cardiac surgery requiring CPB was 0.88 L/h/70kg compared to 1.9 L/h/70kg for a 6 month old with asthma.(43) For a 2 year old, the clearance predicted after cardiac surgery requiring CPB was 1.2 L/h/70kg compared to 4.7 L/h/70kg reported in non-cardiac patients.(28) Readily available clinical biomarkers and covariates measured during clinical care were unable to explain the markedly reduced clearance in children who underwent cardiac surgery requiring CPB. More sensitive and specific measures of cardiac physiology, organ perfusion and/or organ function are likely needed for such a complex and heterogeneous population. Further, our findings are in line with previous studies, which have also shown marked alterations in drug clearance and/or volume are common in children undergoing cardiac surgery requiring CPB.(25–27)

Due to this markedly reduced clearance in children after cardiac surgery requiring CPB, typical recommended aminophylline doses for children will be inappropriate. The predicted steady-state serum concentration using the FDA recommended continuous infusion rate of 1 mg/kg/h in a 2 year old after cardiac surgery requiring CPB is 31 mg/L, which is potentially toxic.(28) To develop optimized aminophylline dosing regimens for children undergoing cardiac surgery requiring CPB, the final pharmacokinetic model was used to perform Monte Carlo simulations (Table 3). Both intermittent dosing and continuous infusion regimens were considered to allow greater flexibility in dose administration for these critically ill post-operative patients in whom an intravenous line for a continuous infusion may not be available. The optimized doses are predicted to achieve target drug serum concentrations of 5-10 mg/L in >60% of patients and minimizes the risk of serum concentrations >20 mg/L. However, variability in exposure still existed, and therapeutic drug monitoring will be required to confirm adequate exposure. To help providers further personalize the dose for a patient based on therapeutic drug monitoring, model-based dosing support tools that apply Bayesian methods and incorporate the developed pharmacokinetic model along with patient-specific characteristics and drug serum concentrations would be valuable.(44) Such model-based dosing support tools are being developed for vancomycin in adults and children. (45,46)

The current pharmacokinetic analysis took advantage of theophylline serum concentrations measured as part of a prospective randomized controlled trial examining whether aminophylline administration reduced the incidence of AKI in children after cardiac surgery requiring CPB.(29) The randomized controlled trial did not show a clinical benefit in terms

of AKI development in the aminophylline group. However, aminophylline was initiated up to 4 hours after the completion of surgery, and AKI had already occurred at the time of randomization in >25% of patients. This early onset of AKI is consistent with previous work, which has demonstrated AKI development within 2 hours after initiation of CPB.(4) Therefore, earlier administration of aminophylline, when ischemic injury is ongoing, may be necessary. Previous randomized controlled studies that have shown a benefit of aminophylline in neonates with perinatal asphyxia all started aminophylline immediately after birth.(14–16) Further clinical studies are needed to examine the potential benefit of earlier theophylline exposure before the initiation of cardiac surgery and CPB. The pharmacokinetic insight gained from the current study can be used to help design any future studies examining aminophylline use in children undergoing cardiac surgery requiring CPB.

Limitations of the current analysis include the use of single center data and sparse pharmacokinetic sampling. However, the population pharmacokinetic approach is well-designed to handling sparse sampling datasets, and all data was rigorously collected as a part of a prospective clinical trial. An additional limitation includes the lack of validation group for analysis due to the relatively small sample size and wide-age range of patients available for study. Therefore, further validation of our model is warranted. Lastly, extrapolating the developed pharmacokinetic model to older children (i.e. >12 years) is not recommended as the power maturation model of clearance implemented allows clearance to continue to rise and can exceed adult values at older ages. A sigmoid $E_{\max}$ model would offer the added benefit of an asymptotic approach to adult maturation (and can never exceed adults) and has been used to describe the maturational changes in the clearance of other drugs metabolized by CYP450s.(47) However, data from the current study did not support a sigmoid $E_{\max}$ model. This may be due to the fact that the majority of patients in the current study were < 1 year (49/71 patients), yet the maturation of CYP1A2 appears to continue after the first year of life.(48,49) In addition, maturation may be altered in a chronically ill population such as children with cardiac disease. Nonetheless, the model developed in the current study was able to adequately describe theophylline pharmacokinetics across the ages studied and no systematic bias was seen in simulation based predictive checks (Figure 2).

Conclusions

In children after cardiac surgery requiring CPB, weight and age significantly impact theophylline pharmacokinetics. Compared to non-cardiac children, theophylline clearance is markedly reduced, and lower doses will be needed to achieve target drug serum concentrations of 5-10 mg/L. Due to remaining inter-patient variation, dose adjustments may be required and can be guided by therapeutic drug monitoring. Additional pharmacokinetic studies are needed in children undergoing cardiac surgery requiring CPB given the frequent alterations in drug disposition described in this vulnerable population.

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Figure 2.
Goodness of fit plots of final pharmacokinetic model. Solid line indicates the line of unity.
Dashed line indicates loess smooth.

Figure 3. Normalized prediction distribution errors (NPDE) of the final pharmacokinetic model. (a) Kernel density plot of NPDE with a normal, Gaussian distribution overlaid for comparative purposes. NPDE versus (b) time after dose, (c) weight, and (d) age. Dotted lines represent the 5% and 95% of a standard normal distribution (i.e. 90% of npde should fall between this range). Dashed line indicates loess smooth of NPDE.

Table 1

Patient Demographics (n = 71)

	Median or No.	90% Range
Age, y	0.4	0.02 – 9.8
Pre-operative weight, kg	5.8	2.7 – 30.2
Female, n (%)	32 (45%)	-
Race, n (%)		
White	59 (83%)	
Black	2 (3%)	
Asian	8 (11%)	
Other or Unknown	2 (3%)	
Hispanic ethnicity, n (%)	25 (35%)	
eGFR pre-op, ml/min per 1.73m ²	68.8	31.8 – 165.4
RACHS-1 category, n (%)		
Category 1	1 (1%)	
Category 2	19 (27%)	
Category 3	25 (35%)	
Category 4	25 (35%)	
Category 5	1 (1%)	
Cardiopulmonary Bypass Time, min	129	49 - 298
VIS first 24 h post-operative	8	0 – 15

eGFR, estimated glomerular filtration rate calculated using 'original' Schwartz formula(32); RACHS-1, Risk Adjustment in Cardiac Surgery - categories 1 to 6; VIS, Vasoactive Inotropic Score - range 0 to >25.

Table 2

Final population PK model parameter estimates and bootstrap results.

Population PK Parameters	Final Model		Bootstrap (n=1000)	
	Estimate	%SE	Median	95% CI
$CL_{\text{typical}} (L/h)^1$	0.130	4.6	0.129	0.116 – 0.142
Exponent for Age _v effect	0.22	11.5	0.22	0.17 – 0.26
$V_{\text{typical}} (L)^2$	2.96	4.9	2.94	2.67 – 3.25
Interindividual variability				
CL, %CV	31.9	26.0	31.6	22.7 – 40.7
V, %CV	18.8	149	18.8	3.3 – 45.7
Residual variability, %CV	18.4	26.8	17.6	12.2 – 24.7

CL, clearance; V, volume of distribution; %CV, coefficient of variation × 100; %SE, relative standard error × 100; 95% CI, Bootstrap parameter estimate at the 2.5th and 97.5th percentiles.

$$CL_{(L/h)} = 0.13 \times \left(\frac{Weight}{5.8 \text{ kg}} \right)^{0.75} \times \left(\frac{Age}{0.4 \text{ year}} \right)^{0.22}$$

$$V_{(L)} = 2.96 \times \left(\frac{Weight}{5.8 \text{ kg}} \right)$$

Table 3

Optimized Aminophylline Maintenance Dosing Regimens based on Monte Carlo Simulations

	Age					
	1 month	6 month	1 year	2 year	6 year	10 year
Intermittent Dosing every 6 h						
Intermittent Dose ^a	1.0 mg/kg	1.4 mg/kg	1.6 mg/kg	1.6 mg/kg	1.8 mg/kg	1.8 mg/kg
Trough _{SS} , mg/L						
Median	6.9	7.4	7.4	6.8	6.6	6.6
90% Range ^b	3.7 – 12.9	3.7 – 13.6	3.8 – 13.9	3.5 – 12.9	3.3 – 12.6	3.3 – 12.6
% Trough _{SS} 5-10 mg/L	65%	61%	63%	61%	61%	61%
% Trough _{SS} >20 mg/L	0.1%	0.5%	0.5%	0.4%	0.4%	0.4%
Continuous Infusion						
Infusion Rate	0.16 mg/kg/h	0.20 mg/kg/h	0.22 mg/kg/h	0.22 mg/kg/h	0.26 mg/kg/h	0.26 mg/kg/h
C _{SS} , mg/L						
Median	7.2	7.1	7.2	6.7	6.8	6.8
90% Range ^c	4.0 – 13.1	4.0 – 13.6	3.7 – 12.8	3.5 – 11.9	3.6 – 11.9	3.6 – 11.9
% C _{SS} 5-10 mg/L	65%	68%	65%	61%	64%	64%
% C _{SS} >20 mg/L	0.3%	0.3%	<0.1%	<0.1%	<0.1%	<0.1%

Trough_{SS}, trough serum concentration at steady-stateC_{SS}, serum concentration at steady-state^aDose given intravenous over 30 minutes every 6 hours^bRange in which 90% of concentrations from 1000 simulated children fell