Published in final edited form as:

Anesthesiology. 2015 May ; 122(5): 1002–1009. doi:10.1097/ALN.0000000000000616.

Pharmacokinetics of Epsilon-Aminocaproic Acid in Neonates: Undergoing Cardiac surgery with Cardiopulmonary Bypass

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Abstract

Background—Antifibrinolytic medications such as epsilon-aminocaproic acid (EACA) are used in pediatric heart surgery to decrease surgical bleeding and transfusion. Dosing schemes for neonates are often based on adult regimens, or are simply empiric, in part due to the lack of neonatal pharmacokinetic information. We sought to determine the pharmacokinetics of EACA in neonates undergoing cardiac surgery and to devise a dosing regimen for this population.

Methods—Ten neonates undergoing cardiac surgery with cardiopulmonary bypass were given EACA according to standard practice, and blood was drawn at 10 time points to determine drug concentrations. Time-concentration profiles were analyzed using nonlinear mixed effects models. Parameter estimates (standardized to a 70 kg person) were used to develop a dosing regimen intended to maintain a target concentration shown to inhibit fibrinolysis in neonatal plasma (50 mg/L).

Results—Pharmacokinetics were described using a two compartment model plus an additional compartment for the cardiopulmonary bypass pump. First order elimination was described with a clearance of $5.07 \text{ L/h} \cdot (\text{WT}/70)^{0.75}$. Simulation showed a dosing regimen with a loading dose of

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The authors declare no competing interests.

40 mg/kg, and an infusion of 30 mg/kg/h, with a pump prime concentration of 100 mg/L maintained plasma concentrations above 50 mg/L in 90% of neonates during cardiopulmonary bypass surgery.

Conclusions—EACA clearance, expressed using allometry, is reduced in neonates compared to older children and adults. Loading dose and infusion dose are approximately half those required in children and adults.

Introduction

Epsilon aminocaproic Acid (EACA) is a lysine analogue anti-fibrinolytic drug that has been shown to be effective in reducing bleeding and transfusion associated with cardiac surgery involving cardiopulmonary bypass in adults ¹ and children ^{2,3}. Dosing schemes reported in the literature vary widely and have not always been based on pharmacokinetic data. The pharmacokinetics of EACA in adults undergoing coronary artery bypass surgery have been determined and a dosing scheme to establish and maintain an effective antifibrinolytic concentration in adults (130 mg/L) reported.⁴ Subsequently the same group published a pharmacokinetic analysis for EACA in infants and children up to four years old ⁵ that differed to adults, suggesting maturational changes with age. These authors recommended a dosing scheme for infants and children, using a target concentration of 260 mg/L to account for interindividual variability and ensure the achievement of the adult effective concentration 130 mg/L in the majority of children.

Neonates have significantly different pharmacokinetic and pharmacodynamic parameters than adults and older children.^{6,7} EACA is a drug that is cleared through the kidney and glomerular filtration rate (GFR) is approximately 30% that of the adult rate in the term neonate and matures over the first few years of life.⁸ Although there is no available evidence of harm produced by current dosing regimens, the use of dosing schemes suitable for children or adults may produce unnecessarily high drug concentrations in neonates with unpredictable effects on fibrinolysis. Since neonates represent a high proportion of those undergoing congenital heart surgery, and the use of EACA is widespread in this population, it is important to establish the pharmacokinetics of EACA in neonates undergoing cardiac surgery and cardiopulmonary bypass.

The concentration of EACA required to inhibit fibrinolysis in adult plasma in vitro was originally described to be 130 mg/L in 1962.⁹ This was confirmed as the effective concentration by Nielsen (VG Nielsen, MD, Department of Anesthesiology, University of Alabama, Birmingham, AL) et al using thromboelastography in 2007.¹⁰ Recently we have shown that neonates require a lower concentration of EACA (50mg/L) to inhibit fibrinolysis ¹¹. This is consistent with the immaturity of the fibrinolytic system at birth.^{12–15}

We studied the pharmacokinetics of EACA in neonates undergoing elective cardiac surgery using cardiopulmonary bypass in order to characterize pharmacokinetics in this age group. We then applied these findings to model a suggested dosing regimen for this population.

Materials and Methods

Study approval was granted by the Research Subjects Review Board of the University of Rochester (Rochester, NY, USA). Consent was obtained from parents of 10 term neonates scheduled to undergo elective palliative or corrective cardiac surgery using cardiopulmonary bypass. Exclusion criteria were: history of significant coagulopathy or hemostatic transfusion, known or suspected sensitivity to EACA, mass less than 2.5 kg, emergency surgery. All neonates received general anesthesia with IV induction using fentanyl and pancuronium for neuromuscular blockade. Anesthesia was maintained with additional fentanyl (25–100 mcg/kg) and isoflurane (0 – 0.8%). A radial arterial line and right internal jugular catheters were placed after endotracheal intubation.

Study Protocol

Prior to initiation of bypass, 400 units/kg of unfractionated heparin was administered via the central line. Additional heparin was administered to maintain an activated clotting time (ACT+, International Technodyne Corporation, Edison, NJ) of 480 sec. Bypass was conducted using either a COBE Century Heart-Lung Machine (COBE Cardiovascular, Arvada, CO) or a Terumo System 1 Heart Lung Machine (Terumo Corporation, Tokyo, Japan). The circuit consisted of 3/16 inch x 1/4 inch tubing (Medtronic Inc., Minneapolis, Minnesota) for the arteriovenous loop, and a roller pump with a 3/8" raceway was used in the arterial position. An Rx05 oxygenator with hardshell reservoir (Terumo Corporation, Tokyo, Japan) and Affinity Pediatric Arterial Line Filter (Medtronic Inc.) were used. The oxygenator was coated with poly-2-methoxyethylacrylate. The bypass prime consisted of 200 mg/kg mannitol, 1000 IU heparin, 25 mg/kg Cefazolin, methylprednisolone 30 mg/kg, 10–15 meq 8.4% Sodium Bicarbonate, and approximately 200 mL of balanced crystalloid solution (Normosol-R, Hospira, Inc., Lake Forest, IL, USA). Fifty mL of 25% albumin and one unit (180–220 mL) of washed packed erythrocytes were added to produce a prime hematocrit of approximately 35% and a total prime volume of 430 to 480 mL. All neonates underwent ultrafiltration during bypass to increase the hematocrit prior to weaning. After separation from bypass, aliquots of residual volume from the pump were administered to optimize the hemodynamic status. No neonate received additional red cells or blood products prior to the end of the study period.

EACA was administered according to a variation of the dose recommended by Ririe (DG Ririe, MD, Department of Anesthesiology, Wake Forest University, Winston-Salem, NC) et al ⁵ for infants and children: 75 mg/kg was administered over 10 minutes after induction of anesthesia, immediately followed by an infusion of 75mg/kg/h until the administration of protamine after ceasing cardiopulmonary bypass. The prime dose was based on the volume of the pump instead of patient weight as suggested by Ririe: 250 mcg was added to the pump reservoir for each mL of prime volume. Blood flow rate through the cardiopulmonary bypass (CPB) pump was noted at approximately 10 minute intervals.

EACA Assay

Blood was drawn from either the arterial line (before and after bypass) or the pump manifold (arterial-venous shunt, during bypass) for determination of EACA concentration at the

following times: baseline (after induction), 3 minutes after the loading dose finished, immediately before commencing bypass, 5 minutes after commencing bypass, after one hour of bypass, just before weaning from bypass, just before stopping the infusion, and 30, 90 and 180 minutes after the infusion was stopped. A sample of the mixed ultrafiltrate was also collected for EACA measurement. In addition to the EACA draws, blood was drawn for thromboelastography at baseline and a d-dimer and thromboelastogram were done after protamine administration. All EACA samples were immediately placed on ice, and upon completion of the sample set were separated by centrifugation (1000 g at 4 °C). The plasma fraction was stored at -70 °C pending drug assay.

EACA concentrations were determined by gas chromatography-mass spectrometry as follows: Norleucine (12.5 ug) was added as an internal standard to each plasma sample (50 uL). Samples were acidified with acetic acid and poured over columns of cation exchange resin (AG 50W-X8, Bio-Rad, Hercules CA, USA), which retained the amino acids. The columns were washed with water, then the amino acids were eluted with 4M NH₄OH. The eluates were dried in a vacuum centrifuge and the amino acids were converted to *tert*-butyldimethylsilyl esters by adding equal volumes of acetonitrile and N-methyl-N-*t*-butyldimethylsilyl-trifluoroacetamide containing 1% *t*-butyldimethylchlorosilane (Regis Technologies, Morton Grove, IL) and heating for 1 h at 70 °C. Amino acid derivatives were separated by gas chromatography (Agilent 6890 with HP-1 column, Agilent Technologies, Santa Clara, CA) and detected with a mass selective detector (Agilent 5973). Concentrations of aminocaproic acid were determined from the ratio of the area under the curve of the aminocaproic acid peak to the area under the curve of the norleucine peak (*m/z* of 200 for both peaks). A standard curve was run with each set of samples to determine the concentrations from these ratios. The standard curves were prepared with plasma samples from subjects who had never received aminocaproic acid. The standards were treated exactly as the other samples except that varying amounts of aminocaproic acid were added before processing. The lower limit of quantification for EACA was 2 mcg/mL and the precision (coefficient of variation) was <10%.

Pharmacokinetic analysis

Population parameter estimates were obtained using non-linear mixed effects modeling (NONMEM 7.3, Globomax LLC, Hanover, MD). This software accounts for population parameter variability (between subjects) and residual variability (random effects) as well as parameter differences predicted by covariates (fixed effects). The population parameter variability (or between subject variability, BSV) for structural model parameters was modelled by a proportional variance model. Residual unknown variability was modelled using additive and proportional terms. The first order conditional interaction estimate method with differential equations using ADVAN6 was used to estimate population mean parameters, between subject variance and residual variance. Convergence criterion was 3 significant digits.

The population parameter variability was modelled in terms of random effect (η) variables. Each of these variables was assumed to have mean 0 and a variance denoted by ω^2 , which was estimated.

Structural model

Four different study periods, with potential to impact EACA clearance, were considered: prior to initiation of bypass, during bypass, during circulatory arrest, and after separation. The pre- and post-bypass periods were treated as one condition (clearance was assumed to be similar). Structural models considered included those with one or two distribution compartments. An additional compartment was used to characterize the bypass circuit. Elimination was investigated using both first order and also using Michaelis Menton kinetics.

A step change in clearance during bypass compared to other periods was also explored. For example, the time course of EACA concentrations in each compartment has been expressed using 3-compartment model (plasma, periphery and CPB device) using first order elimination with differential equations 1–3 (Figure 1)

$$\frac{dC1}{dt} = \text{infusion rate} - Q \cdot (C1 - C2) - \text{Flow} \cdot (C1 - C3) - CL \cdot C1 \quad \text{Equation 1}$$

$$\frac{dC2}{dt} = Q \cdot (C1 - C2) \quad \text{Equation 2}$$

$$\frac{dC3}{dt} = \text{Flow} \cdot (C1 - C3) \quad \text{Equation 3}$$

C1 is the concentration in the plasma; C2 is the concentration in the periphery and C3 is the concentration of EACA in the CPB device. The distributional clearance between the plasma and the periphery is represented by Q, and CL is the clearance of drug from the central compartment Flow is the zero order rate of plasma flow between the CPB device and the central compartment. The amount of drug and volume in the cardiopulmonary circuit was recorded for initial conditions. The CPB pump was simply turned off or on using a dichotomous variable (1 or 0) in the data set.

Covariate analysis

The covariance between two elements of η (e.g. CL and V) is a measure of statistical association between these two variables. Their covariance is related to their correlation (R) i.e.

$$R = \text{covariance} / \sqrt{(\omega_{CL}^2 \times \omega_V^2)}$$

The covariance of parameter variability was incorporated into the model.

The parameter values were standardised for a body weight of 70 kg using an allometric model^{16,17}.

$$P_i = P_{std} \cdot \left(W_i / W_{std} \right)^{PWR}$$

where P_i is the parameter in the i th individual, W_i is the weight in the i th individual and P_{std} is the parameter in an individual with a weight W_{std} of 70 kg. This standardisation allows comparison of neonatal parameter estimates with those reported for adults. The *PWR* exponent was 0.75 for clearance, 0.25 for half-times and 1 for distribution volumes.¹⁸

The shift in total clearance during cardiopulmonary bypass was also explored using a scaling factor for clearance that enabled comparison to clearance after bypass.

$$CL_i = CL_{std} \cdot FCL \cdot FHA \cdot \left(W_i / W_{std} \right)^{0.75}$$

During intervals of circulatory arrest, the perfusion of the clearing organs and, thus, the total body clearances (CL and Q) were assumed to be zero. This was achieved by fixing a further factor (factor for hypothermic arrest) implemented during periods of deep hypothermic cardiac arrest (DHCA) to 0.

Quality of fit

The quality of fit of the pharmacokinetic model to the data was sought by NONMEM's objective function and by visual examination of plots of observed *versus* predicted concentrations. Models were nested and an improvement in the objective function was referred to the Chi-squared distribution to assess significance e.g. an objective function change (OBJ) of 3.84 is significant at $\alpha = 0.05$ for one additional parameter and an OBJ change of 6.64 is significant at $\alpha = 0.01$ for one additional parameter. We used bootstrap methods, incorporated within the NONMEM program, to provide a means to evaluate parameter uncertainty; these are more reliable than standard errors that assume a symmetric parameter space.¹⁹ A total of 1000 replications were used to estimate parameter confidence intervals. A visual predictive check²⁰, a modeling tool that estimates the concentration prediction intervals and graphically superimposes these intervals on observed concentrations after a standardized dose, was used to evaluate how well the model predicted the distribution of observed plasma concentrations. Simulation was performed using 1000 subjects with characteristics taken from studied children. For data such as these where covariates such as dose and weight are different for each patient, we used a prediction corrected visual predictive check.^{21,22}

Simulation

Attention was then given to calculating the ideal dose to establish and maintain the putative effective concentration (50 mg/L) in 90% typical patients (e.g., neonate 3.5 kg, 1 week of age, Hemoglobin 12 mg/dL, pump flow 500 mL/min, Pump volume 450 mL, Creatinine 0.7 mg/dL). Qualitatively, we assumed that concentrations moderately > 100 mg/L were preferred to concentrations < 50 mg/L. Based on the final pharmacokinetic model parameter estimates, loading doses and ideal steady-state IV infusion rates were calculated. Dosing

schemes were selected to rapidly achieve and maintain the target plasma concentration (100 mg/L). For the simulations, we assumed that, at time zero, the IV loading dose was started simultaneously with anaesthesia induction. After 10 minutes the IV loading dose was switched to a maintenance infusion. CPB (with a priming dose loaded into the CPB circuit) was started at 1 hour after the loading dose. The infusion ran for 3.2 h. Hypothermic cardiac arrest was 30 min duration from 2.3–2.8 h after anesthesia induction.

The NONMEM code is available upon request.

Results

All neonates completed the study. Demographics and surgical characteristics are listed in Table 1. One patient became hemodynamically unstable prior to initiation of bypass and did not have pharmacokinetic draws at every time period. One patient received a higher dose of EACA in the pump prime (250 mg) than called for by the protocol (110 mg) due to miscommunication. Otherwise all medication administrations and blood draws were carried out according to protocol. The analysis was based on 10 neonates with 85 observations. No observations after study drug administration were below the lower limit of quantification. The final model used two body compartments and a third compartment for the bypass pump, first order elimination and an increase (described by the parameter, Factor for Clearance) in total clearance during bypass. Objective function changes associated with model building are shown in Table 2. The use of nonlinear kinetics (Michaelis Menton) decreased the objective function marginally (OBJ 0.818). Models using allometric scaling did not differ significantly from those with either no scaling or per kilogram linear scaling. The linear per kilogram model fit the data nearly identically to the allometric model. The value for clearance in that model was 0.2 L/kg/h.

Clearance increased during CPB by a factor of 2.08 (95%CI 1.44, 3.86) compared to that observed after CPB (OBJ 8.725, $p < 0.005$). Elimination clearance and between-compartment clearance were set to approach zero during deep hypothermic arrest. Estimating a parameter to describe reduced CL and Q during this period reduced the objective function by 5.649 (0.01 $p > 0.05$). Consequently this parameter (Factor for Hypothermic Arrest) was excluded from the final model. Pharmacokinetic parameter estimates are reported in Table 3 and 4. The correlation of between parameter variability introduced to increase stability of the model in shown in Table 5. PC-visual predictive check plots, used to demonstrate goodness of fit, are shown in Figure 2. Standard diagnostic plots showing predictions vs. observations are shown in Figure 3.

The modified Ririe dosing scheme was effective in establishing and maintaining concentrations of at least 130 mg/L for the period of cardiopulmonary bypass in 90% of samples. Mean EACA concentrations for the three sampling times during CPB were 262 SD 105 mg/L, 268 SD 137 mg/L, and 262 SD 78 mg/L. Fibrinolysis at the end of bypass was completely suppressed as measured by thromboelastography (Ly30 = 0%, 0 – 0.9% [median, range]), but d-dimers were mildly elevated in 6 of 10 patients (0.61 mg/L, 0.22–1.23). The mean ultrafiltrate concentration of EACA was 262 SD 120 mg/L, not significantly different from the plasma concentrations during CPB.

Simulation suggested a priming dose of 0.1 mg EACA per 100 mL of blood prime, an IV loading dose of 40 mg/kg, with an infusion of 30 mg/kg/h (Figure 4). This dosing regimen maintained a steady state concentration of 100 mg/L with a concentration >50 mg/L in 90% of simulated neonates.

Discussion

This current data analysis confirms first order elimination, reduced clearance in neonates and suggests an increased clearance during bypass. Two previous studies have been published characterizing the pharmacokinetics of EACA during bypass, one of which was in adults and another in children.^{4,5} Both studies also used a two-compartment model with first order elimination in patients undergoing CPB. Clearance, expressed using allometry, was reduced in neonates relative to older children and adults. Estimates of clearance in both infants (2–24 months, 6.7–11.8 kg) with normal renal function presenting for craniofacial surgery ($CL\ 12.7\ L/h \cdot (WT/70)^{0.75}$)²³ and in infants and children (9 months–4 years, 6.8–18.9 kg) presenting for cardiac surgery ($9.22\ L/h \cdot (WT/70)^{0.75}$)⁵ were higher than our estimate of $5.07\ L/h \cdot (WT/70)^{0.75}$ in neonates. Adult clearance of 7.5 L/h after aortocoronary bypass surgery is also greater than that currently observed in neonates.⁴ The elimination of EACA is known to occur largely through the kidneys, where it is rapidly excreted in the urine. It has been reported that the clearance of EACA is within similar ranges with that of creatinine clearance, suggesting filtration as the primary mechanism of EACA excretion.⁹ Renal function of term healthy neonates is approximately one third that of adults, as mature rates of renal blood flow and glomerular filtration are not reached until after one to several years of life.⁸ This maturation profile has been described using the Hill equation demonstrating that rapid maturation that reaches 50% of mature values by 47 weeks postmenstrual age after standardization using allometric scaling. The current analysis was limited to 10 neonates and the maturation profile for EACA clearance could not be mapped. Additionally, neonates undergoing CPB are at risk for preoperative renal dysfunction due to low systemic cardiac output. This renal dysfunction can be difficult to quantify because regular measures of renal function (e.g. serum creatinine, urine output, and the Schwartz equation for calculating creatinine clearance) are inaccurate in these patients.²⁴

We discerned a clearance step increase during bypass compared to that observed after bypass. Adults had clearance decreased by 91% during CPB⁴, while clearance in infants and children was reduced 38% during CPB⁵. Given that essentially all neonates requiring surgery for congenital heart disease in the neonatal period suffer from compromised systemic perfusion due to parallel circulations, single ventricle physiology and/or aortic obstruction, it is possible that improved renal blood flow and arterial blood oxygenation during CPB increase renal blood flow and clearance of EACA in neonates during this period. Ultrafiltration employed during CPB could also affect clearance. However, EACA concentrations in the ultrafiltrate were similar to the plasma concentrations during bypass, so it is unlikely that ultrafiltration has a significant effect. Mannitol added to the pump also acts as an osmotic diuretic. Although others have delineated clearance changes with CPB and again after CPB^{4,5}, we had insufficient data from the pre-CPB period to distinguish the pre-CPB clearance from post-CPB changes.

This study is limited by the small number of patients and samples, by the variety of procedures and differences in the conduct of CPB. Our sample size was necessarily limited by the available population and the willingness of parents to consent. Few data from the pre-bypass period were available for analysis. We were unable to account for differences in temperature management during CPB, and it is possible that profound hypothermia has an influence of clearance. Unfortunately the elimination half-life of 6.2 h precluded investigation of these covariates during the limited CPB duration. Research in surgery for congenital heart disease is almost always confounded to some extent by the heterogeneity of the patient population and procedures. Our population is at least reflective of the somewhat more homogenous group of neonates.

We have shown that a dosing scheme based on pharmacokinetic parameters determined in infants and children was effective in establishing and maintaining the target concentration of 130 mcg/mL in neonates. However, neonates have reduced clearance and a lower target concentration of 50 mg/L. Consequently a loading dose of 40 mg/kg and an infusion of 30 mg/L are adequate to achieve evidence-based therapeutic concentrations during bypass. A loading dose in the CPB prime was required to maintain this target concentration. This CPB prime dose was unnecessary in older children given tranexamic acid in a study published in 2013.²⁵ However the relative prime volume of 450 mL will have greater impact in a 3 kg neonate with a volume of distribution of just over one liter compared to the 18–19 kg children included in the prior study. Figure 3 shows a residual consequent slight drop in concentration as CPB is initiated. Subsequent studies to ensure the clinical efficacy of this dosing regimen will be necessary to confirm this recommendation.

Acknowledgments

Funding: Support was provided solely from institutional and/or departmental sources.

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Figure 1.

Model for flux of ε-aminocaproic acid (EACA) during neonatal heart surgery. The loading dose and EACA infusion were given into the central compartment with volume V1 and concentration C1. Blood flow was recorded throughout cardiopulmonary bypass (CPB); these were converted to plasma flow based on hemoglobin concentration. The inter-compartmental clearance (Q) linked the central compartment to the peripheral compartment that had volume V2 and concentration C2. The volume in the CPB pump had the concentration C3. Clearance (CL) was allowed to switch from on to off during circulatory arrest.

Figure 2.

Visual predictive check for the ϵ -aminocaproic acid 2-compartment model. Observed concentrations are on left (A). Prediction percentiles (10%, 50%, and 90%) for observations (lines with symbols) and predictions (lines) with 95% confidence intervals for prediction percentiles (gray shaded areas) are on right (B). Both plots show median and 90% intervals (solid and dashed lines).

Figure 3.

Goodness of Fit Plots. Observed Vs Predicted EACA concentrations for all data points (A), bypass only (B), and post-bypass (C). Line of fit constructed using *supsmu* (R Language and environment for statistical computing, Vienna, Austria)

Figure 4.

Simulation using an IV loading dose of 40 mg/kg with an infusion of 30 mg/kg/h, and a prime dose of 0.1 mg ϵ -aminocaproic acid (EACA) per 100 mL of prime volume in the bypass pump, in a 3.5 kg neonate of 1 week age. This dosing regimen maintained a steady state concentration of 100 mg/L with a concentration >50 mg/L in 90% of simulated neonates. CPB = cardiopulmonary bypass; DHCA = deep hypothermic circulatory arrest

Table 1

Demographic and Procedure Data.

#	Age (days)	Weight (kg)	Sex	Procedure	CPB (min)	DHCA (min)
1	6	3.2	F	BT shunt/ Patent Ductus Arteriosus ligation	70	0
2	20	3.8	M	Tetralogy of Fallot repair	122	0
3	12	3.5	F	Arch reconstruction	69	31
4	6	3.5	M	Arterial switch/Coarctation repair	173	22
5	18	3.6	M	Norwood/Sano	149	13
6	8	3.8	F	BT shunt/ Pulmonary Valvotomy	74	0
7	10	2.7	F	Arch Reconstruction/ ventricular septal defect closure	83	29
8	3	2.7	M	Norwood/Sano	169	15
9	23	2.8	M	Tetralogy of Fallot repair	107	0
10	7	3.7	M	Norwood	110	58

BT = Blalock-Taussig, CPB = Cardiopulmonary Bypass, DHCA = Deep Hypothermic Circulatory Arrest.

Table 2

Objective function changes associated with model building.

	Model	Objective Function
1	1-compartment, no size standard	858.925
2	1-compartment, size per kilogram	858.772
3	1-compartment, allometric scaling	857.571
4	2-compartment, no size standard	830.912
5	2-compartment, size per kilogram	829.120
6	2-compartment, allometric scaling	829.122
7	2-compartment, size per kilogram, FCL during CPB	821.762
8	2-compartment, allometric scaling, FCL during CPB **	820.360
9	2-compartment, Michaelis Menten, allometric scaling, FCL during CPB	819.542
10	2-compartment, allometric scaling, FCL during CPB, FHA during DHCA	814.711

** Final model. CPB = Cardiopulmonary Bypass, FCL = scaling Factor for Clearance, FHA = Factor for Hypothermic Arrest.

Table 3

Standardised EACA population pharmacokinetic parameter estimates

Parameter	Typical 3 kg neonate	Allometric Estimate	%BSV	95%CI
CL	0.48	5.07	31.5	3.54, 6.77
V1	0.23	6.99	53.1	1.82, 13.9
Qstd	4.41	46.8	1.32	17.6, 152
V2std	1.08	25.3	26.2	16.19, 37.2
FCL	2.08	2.08	-	1.26, 3.08
Residual Error	Additive mg.L ⁻¹	0.005	-	0.0033, 0.092
	Proportional %	27.6		21.3, 31.7

Allometric parameters are expressed as $L/h \cdot (WT/70)^{0.75}$ for CL and Q and as $L \cdot (WT/70)$ for V1 and V2. Estimates for the 3 kg neonate are expressed as L/h for CL and Q and as L for V1 and V2.

(BSV = between subject parameter variability, CI = confidence interval, CL = clearance, FCL = a scaling factor representing the shift in clearance during bypass, Qstd = standardized distributional clearance of drug from the central to peripheral compartment, V1 = Volume of Distribution of Central Compartment, V2std = Volume of distribution of the peripheral compartment).

Table 4

Derived pharmacokinetic parameterisation

A	0.1227 mg/L	V₁	6.99 L	T_{1/2α}	6 min
B	0.0204 mg/L	K₁₀	0.7253 h ⁻¹	T_{1/2β}	6.2 h
alpha (α)	8.635 h ⁻¹	K₁₂	6.6953 h ⁻¹		
beta (β)	0.1114 h ⁻¹	K₂₁	1.3258 h ⁻¹		

A, B, alpha and beta are hybrid constants used to describe elimination in a two-compartment model:

$$Concentration=Ae^{-\alpha t}+Be^{-\beta t}$$

T_{1/2α} is the distribution half-life while T_{1/2β} is the elimination half-life

The two-compartment model can also be parameterised using micro-constants (V₁, K₁₀, K₁₂ and K₂₁) where V₁ is the volume of distribution of central compartment; K₁₂ is the distribution rate constant from the central compartment to the peripheral compartment; K₂₁, the distribution rate constant from the peripheral compartment to the central compartment; K₁₀, the distribution rate constant from the central compartment to the outside

$$\begin{aligned} CL &= K_{10} \times V_1 \\ Q &= K_{12} \times V_1 \\ V_2 &= K_{12} / K_{21} \times V_1 \end{aligned}$$

Table 5

The correlation of parameter between-subject variability

	CL	V1	Q	V2
CL	1			
V1	0.670	1		
Q	-0.998	-0.663	1	
V2	0.861	0.953	-0.854	1

CL = clearance, Q= distributional clearance of drug from the central to peripheral compartment, V1 = Volume of Distribution of Central Compartment, V2 = Volume of distribution of the peripheral compartment