Pharmacokinetics of ε-Aminocaproic Acid in Neonates Undergoing Cardiac Surgery with Cardiopulmonary Bypass

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ABSTRACT

Background: Antifibrinolytic medications such as ε-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. The authors 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 l/h × $(WT/70)^{0.75}$. Simulation showed a dosing regimen with a loading dose of 40 mg/kg and an infusion of 30 mg · kg^{-1} · h^{-1}, 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 with older children and adults. Loading dose and infusion dose are approximately half those required in children and adults. **(Anesthesiology 2015; 122:1002-9)**

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ε-AMINOCAPROIC acid (EACA) is a lysine analog antifibrinolytic drug that has been shown to be effective in reducing bleeding and transfusion associated with cardiac surgery involving cardiopulmonary bypass (CPB) 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 4 yr old[5] that differed to adults, suggesting maturational changes with age. The 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 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. Because neonates represent a high proportion of those undergoing congenital heart surgery, and the use of EACA is widespread in this

What We Already Know about This Topic

- ε-Aminocaproic acid (EACA) is a lysine analog antifibrinolytic drug that has been shown to be effective in reducing bleeding and transfusion associated with cardiac surgery involving cardiopulmonary bypass in adults and children.
- Because neonates represent a high proportion of those undergoing congenital heart surgery, it is important to establish the pharmacokinetics of EACA in neonates undergoing cardiac surgery and cardiopulmonary bypass.

What This Article Tells Us That Is New

- ε-Aminocaproic acid clearance, expressed using allometry, is reduced in neonates undergoing elective cardiac surgery compared with older children and adults. Loading dose and infusion dose are approximately half those required in children and adults.

Submitted for publication April 18, 2014. Accepted for publication January 27, 2015. From the Departments of Anesthesiology (M.P.E., D.M.S.), Surgery (G.M.A., R.E.A.), Pediatrics (J.M.C.), and Neurology, Center for Human Experimental Therapeutics (C.V.), University of Rochester School of Medicine and Dentistry, Rochester, New York; and Department of Anaesthesiology, University of Auckland, Auckland, New Zealand (B.A.).

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population, it is important to establish the pharmacokinetics of EACA in neonates undergoing cardiac surgery and CPB.

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 *et al.*[10] using thromboelastography in 2007. Recently, we have shown that neonates require a lower concentration of EACA (50 mg/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 CPB 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). Consent was obtained from parents of 10 term neonates scheduled to undergo elective palliative or corrective cardiac surgery using CPB. Exclusion criteria were history of significant coagulopathy or hemostatic transfusion, known or suspected sensitivity to EACA, mass less than 2.5 kg, or emergency surgery. All neonates received general anesthesia with IV induction using fentanyl and pancuronium for neuromuscular blockade. Anesthesia was maintained with additional fentanyl (25 to 100 μg/kg) and isoflurane (0 to 0.8%). A radial arterial line and right internal jugular catheters were placed after endotracheal intubation.

Study Protocol

Before 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 (International Technidyne Corporation, USA) of ≥480 s. Bypass was conducted using either a COBE Century Heart-Lung Machine (COBE Cardiovascular, USA) or a Terumo System 1 Heart Lung Machine (Terumo Corporation, Japan). The circuit consisted of 3/16 inch × ¼″ tubing (Medtronic Inc., USA) 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) 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, 1,000 IU heparin, 25 mg/kg cefazolin, methylprednisolone 30 mg/kg, 10 to 15 mEq 8.4% sodium bicarbonate, and approximately 200 ml of balanced crystalloid solution (Normosol-R, Hospira, Inc., USA). Fifty milliliters of 25% albumin and 1 unit (180 to 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 before 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 before the end of the study period.

EACA was administered according to a variation of the dose recommended by Ririe *et al.*[5] for infants and children: 75 mg/kg was administered over 10 min after induction of anesthesia, immediately followed by an infusion of 75 mg · kg^{-1} · h^{-1} until the administration of protamine after ceasing CPB. The prime dose was based on the volume of the pump instead of patient weight, as suggested by Ririe *et al.*[5]: 250 μg was added to the pump reservoir for each milliliter of prime volume. Blood flow rate through the CPB pump was noted at approximately 10-min 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 min after the loading dose finished; immediately before commencing bypass; 5 min after commencing bypass; after 1 h of bypass; just before weaning from bypass; just before stopping the infusion; and 30, 90, and 180 min 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 (1,000*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 μg) was added as an internal standard to each plasma sample (50 μl). Samples were acidified with acetic acid and poured over columns of cation exchange resin (AG 50W-X8, Bio-Rad, USA), which retained the amino acids. The columns were washed with water, and then the amino acids were eluted with 4 M NH_4OH. 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*-*tert*-butyldimethylsilyl-trifluoroacetamide containing 1% *tert*-butyldimethylchlorosilane (Regis Technologies, USA) and heating for 1 h at 70°C. Amino acid derivatives were separated by gas chromatography (Agilent 6890 with HP-1 column; Agilent Technologies, USA) 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

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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 μg/ml, and the precision (coefficient of variation) was less than 10%.

Pharmacokinetic Analysis

Population parameter estimates were obtained using nonlinear mixed effects modeling (NONMEM 7.3; Globomax LLC, USA). 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) for structural model parameters was modeled by a proportional variance model. Residual unknown variability was modeled 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 three significant digits.

The population parameter variability was modeled 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: before 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–Menten kinetics.

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

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

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

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

$C1$ 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.

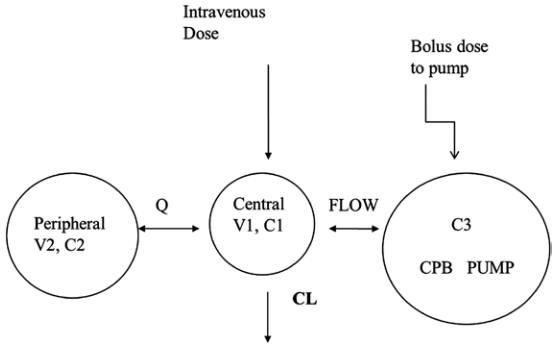

Fig. 1. Model for flux of ε-aminocaproic acid (EACA) during neonatal heart surgery. The loading dose and EACA infusion were given into the central compartment with volume V1 and concentration C1. Blood flow was recorded throughout cardiopulmonary bypass (CPB); these were converted to plasma flow based on hemoglobin concentration. The intercompartmental 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.

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), that is,

$$R = \text{covariance} \Big/ \sqrt{\left(w_{\text{CL}}^2 \, \text{xw}_V^2\right)}$$

The covariance of parameter variability was incorporated into the model.

The parameter values were standardized for a body weight of 70 kg using an allometric model.[16,17]

$$P_i = P_{\text{SD}} - \left(\frac{W_i}{W_{\text{SD}}}\right)^{\text{PWR}}$$

where P_i is the parameter in the ith individual, W_i is the weight in the ith individual, and P_{SD} is the parameter in an individual with a weight W_{SD} of 70 kg. This standardization 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]

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

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

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 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, for example, 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 1,000 replications were used to estimate parameter confidence intervals. A visual predictive check,[20] 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 1,000 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 calculate 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 greater than 100 mg/l were preferred to concentrations less than 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 anesthesia induction. After 10 min, the IV loading dose was switched to a maintenance infusion. CPB (with a priming dose loaded into the CPB circuit) was started at 1 h after the loading dose. The infusion ran for 3.2 h. Hypothermic cardiac arrest was 30 min duration from 2.3 to 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 before 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. OBJs associated with model building are shown in table 2. The use of nonlinear kinetics

Table 1. Demographic and Procedure Data

No.	Age (d)	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.

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(Michaelis–Menten) decreased the objective function marginally (ΔOBJ 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 fits the data nearly identically to the allometric model. The value for clearance in that model was $0.2\ l \cdot kg^{-1} \cdot h^{-1}$.

Clearance increased during CPB by a factor of 2.08 (95% confidence interval, 1.44 to 3.86) compared with that observed after CPB (ΔOBJ 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 tables 3 and 4. The correlation of between-subject parameter variability introduced to increase stability of the model in shown in table 5. Prediction-corrected visual predictive check plots, used to demonstrate goodness of fit, are shown in figure 2. Standard diagnostic plots showing predictions *versus* 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 CPB 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 to 0.9% [median, range]), but D-dimers were mildly elevated in 6 of 10 patients (0.61 mg/l, 0.22 to 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 1 ml of blood prime, an IV loading dose of 40 mg/kg, with an infusion of $30\ mg \cdot kg^{-1} \cdot h^{-1}$ (fig. 4). This dosing regimen maintained a steady state concentration of 100 mg/l with a concentration greater than 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

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; DHCA = deep hypothermic circulatory arrest; FCL = scaling factor for clearance; FHA = factor for hypothermic arrest.

Table 3. Standardized 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)		0.005	—	0.0033, 0.092
Proportional (%)		27.6		21.3, 31.7

Allometric parameters are expressed as $l/h \times (WT/70)^{0.75}$ for CL and Q and as $l \times (WT/70)$ 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; EACA = ε-aminocaproic acid; 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.

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Table 4. Derived Pharmacokinetic Parameterization

A	0.1227 mg/l
B	0.0204 mg/l
α	8.635 h^{-1}
β	0.1114 h^{-1}
V_1	6.99 L
K_{10}	0.7253 h^{-1}
K_{12}	6.6953 h^{-1}
K_{21}	1.3258 h^{-1}
$T_{1/2}\alpha$	6 min
$T_{1/2}\beta$	6.2 h

A, B, α, and β are hybrid constants used to describe elimination in a two-compartment model: Concentration = $Ae^{-\alpha t} + Be^{-\beta t}$. $T_{1/2}\alpha$ is the distribution half-life, while $T_{1/2}\beta$ is the elimination half-life. The two-compartment model can also be parameterized using microconstants (V_1, K_{10}, K_{12}, and K_{21}) where V_1 is the volume of distribution of central compartment; K_{12} is the distribution rate constant from the central compartment to the peripheral compartment; K_{21}, the distribution rate constant from the peripheral compartment to the central compartment; K_{10}, the distribution rate constant from the central compartment to the outside. CL = clearance; Q = intercompartmental clearance; V_2 = volume of the peripheral compartment.

$CL = K_{10} \times V_1$.

$Q = K_{12} \times V_1$.

$V_2 = K_{12}/K_{21} \times V_1$.

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; V_1 = volume of distribution of central compartment; V_2 = volume of distribution of the peripheral compartment.

CPB. Clearance, expressed using allometry, was reduced in neonates relative to older children and adults. Estimates of clearance in both infants (2 to 24 months, 6.7 to 11.8 kg) with normal renal function presenting for craniofacial surgery (CL 12.7 l/h × $(WT/70)^{0.75}$)[23] and in infants and children (9 months to 4 yr, 6.8 to 18.9 kg) presenting for cardiac surgery (9.22 l/h × $(WT/70)^{0.75}$)[5] were higher than our estimate of 5.07 l/h × $(WT/70)^{0.75}$ 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. In addition, neonates undergoing CPB are at risk of 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 with that observed after bypass. Adults had clearance decreased by 91% during CPB,[4] while clearance in infants and children was reduced 38% during CPB.[5] Given that essentially all neonates requiring surgery for congenital heart disease in the neonatal period experience 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 used during CPB could also affect clearance. However, EACA

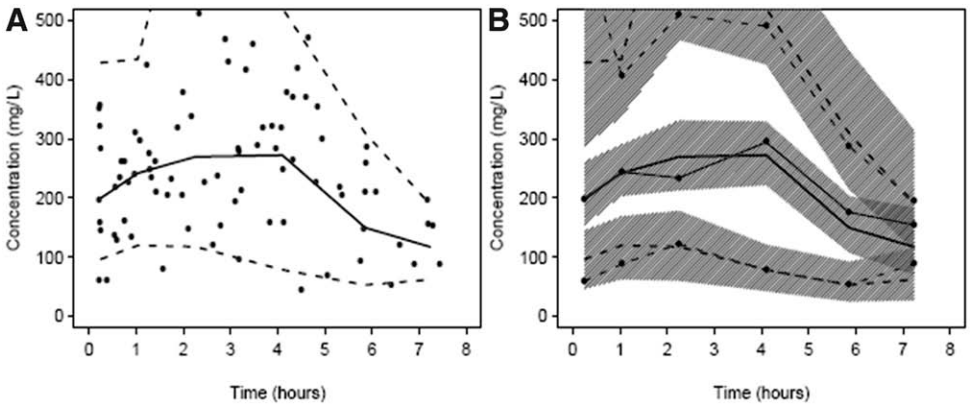

Fig. 2. Visual predictive check for the ε-aminocaproic acid two-compartment model. Observed concentrations are on left (*A*). Prediction percentiles (10%, 50%, and 90%) for observations (*lines with symbols*) and predictions (*lines*) with 95% confidence intervals for prediction percentiles (*gray-shaded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

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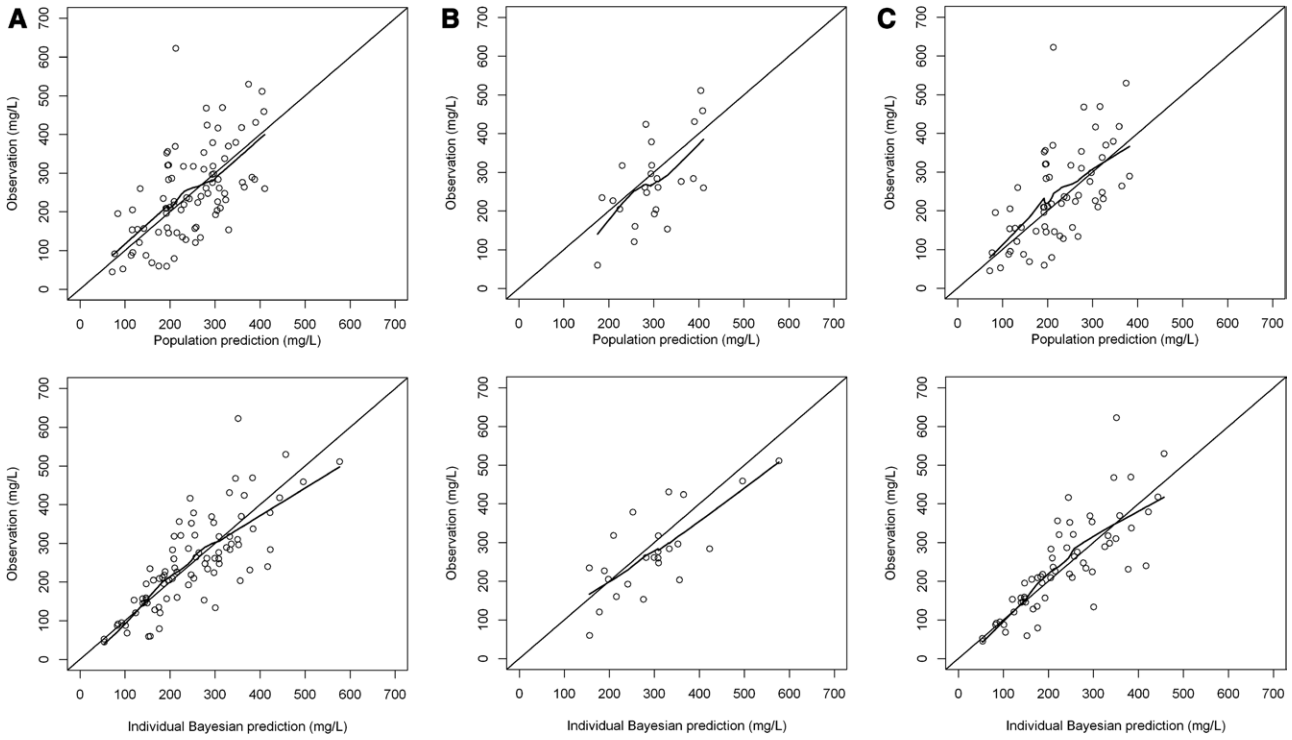

Fig. 3. Goodness of fit plots. Observed *versus* predicted ε-aminocaproic acid concentrations for all data points (*A*), bypass only (*B*), and post-bypass (*C*). Line of fit constructed using supsmu (R Language and environment for statistical computing, Vienna, Austria).

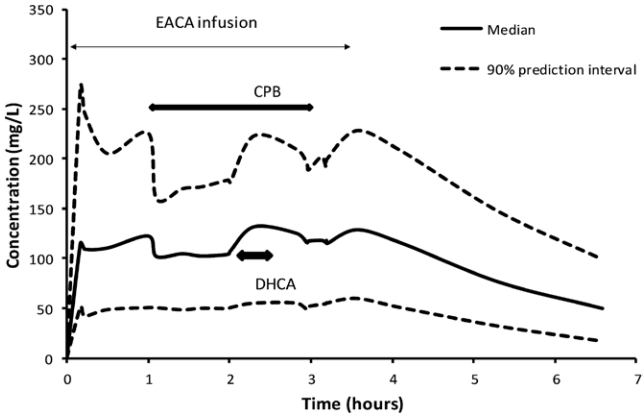

Fig. 4. Simulation using an intravenous loading dose of 40 mg/kg with an infusion of 30 mg · kg^{-1} · h^{-1} and a prime dose of 0.1 mg ε-aminocaproic acid (EACA) per 1 ml of prime volume in the bypass pump, in a 3.5-kg neonate of 1-week age. This dosing regimen maintained a steady state concentration of 100 mg/l with a concentration greater than 50 mg/l in 90% of simulated neonates. CPB = cardiopulmonary bypass; DHCA = deep hypothermic circulatory arrest.

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 by 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 prebypass 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 homogeneous group of neonates.

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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 μg/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 1 l compared with the 18- to 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

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

Competing Interests

The authors declare no competing interests.

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References

1. DelRossi AJ, Cernaianu AC, Botros S, Lemole GM, Moore R: Prophylactic treatment of postperfusion bleeding using EACA. Chest 1989; 96:27–30
2. McClure PD, Izsak J: The use of ε-aminocaproic acid to reduce bleeding during cardiac bypass in children with congenital heart disease. Anesthesiology 1974; 40:604–8
3. Rao BH, Saxena N, Chauhan S, Bisoi AK, Venugopal P: ε-aminocaproic acid in paediatric cardiac surgery to reduce postoperative blood loss. Indian J Med Res 2000; 111:57–61
4. Butterworth J, James RL, Lin Y, Prielipp RC, Hudspeth AS: Pharmacokinetics of ε-aminocaproic acid in patients undergoing aortocoronary bypass surgery. Anesthesiology 1999; 90:1624–35
5. Ririe DG, James RL, O'Brien JJ, Lin YA, Bennett J, Barclay D, Hines MH, Butterworth JF: The pharmacokinetics of ε-aminocaproic acid in children undergoing surgical repair of congenital heart defects. Anesth Analg 2002; 94:44–9
6. Besunder JB, Reed MD, Blumer JL: Principles of drug biodisposition in the neonate. A critical evaluation of the pharmacokinetic-pharmacodynamic interface (Part I). Clin Pharmacokinet 1988; 14:189–216
7. Besunder JB, Reed MD, Blumer JL: Principles of drug biodisposition in the neonate. A critical evaluation of the pharmacokinetic-pharmacodynamic interface (Part II). Clin Pharmacokinet 1988; 14:261–86
8. Rhodin MM, Anderson BJ, Peters AM, Coulthard MG, Wilkins B, Cole M, Chatelut E, Grubb A, Veal GJ, Keir MJ, Holford NH: Human renal function maturation: A quantitative description using weight and postmenstrual age. Pediatr Nephrol 2009; 24:67–76
9. McNicol G, Fletcher A, Alkjaersig N, Sherry S: The absorption, distribution, and excretion of ε-aminocaproic acid following oral or intravenous administration to man. J Lab Clin Med 1962; 59:15–24
10. Nielsen VG, Cankovic L, Steenwyk BL: ε-Aminocaproic acid inhibition of fibrinolysis *in vitro*: Should the 'therapeutic' concentration be reconsidered? Blood Coagul Fibrinolysis 2007; 18:35–9
11. Yurka HG, Wissler RN, Zanghi CN, Liu X, Tu X, Eaton MP; Congenital Heart Surgery Research Interest Group: The effective concentration of ε-aminocaproic acid for inhibition of fibrinolysis in neonatal plasma *in vitro*. Anesth Analg 2010; 111:180–4
12. Albisetti M: The fibrinolytic system in children. Semin Thromb Hemost 2003; 29:339–48
13. Andrew M, Paes B, Milner R, Johnston M, Mitchell L, Tollefsen DM, Powers P: Development of the human coagulation system in the full-term infant. Blood 1987; 70:165–72
14. Ries M, Easton RL, Longstaff C, Zenker M, Corran PH, Morris HR, Dell A, Gaffney PJ: Differences between neonates and adults in tissue-type-plasminogen activator (t-PA)-catalyzed plasminogen activation with various effectors and in carbohydrate sequences of fibrinogen chains. Thromb Res 2001; 103:173–84
15. Ries M, Easton RL, Longstaff C, Zenker M, Morris HR, Dell A, Gaffney PJ: Differences between neonates and adults in carbohydrate sequences and reaction kinetics of plasmin and α(2)-antiplasmin. Thromb Res 2002; 105:247–56
16. Holford NH: A size standard for pharmacokinetics. Clin Pharmacokinet 1996; 30:329–32
17. Anderson BJ, Meakin GH: Scaling for size: Some implications for paediatric anaesthesia dosing. Paediatr Anaesth 2002; 12:205–19
18. Anderson BJ, Holford NH: Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol 2008; 48:303–32
19. Efron B: Bootstrap methods: Another look at the jackknife. Ann Stat 1979; 7:1–26
20. Post TM, Freijer JI, Ploeger BA, Danhof M: Extensions to the visual predictive check to facilitate model performance evaluation. J Pharmacokinet Pharmacodyn 2008; 35:185–202
21. Karlsson MO, Savic RM: Diagnosing model diagnostics. Clin Pharmacol Ther 2007; 82:17–20
22. Bergstrand M, Hooker AC, Wallin JE, Karlsson MO: Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. AAPS J 2011; 13:143–51
23. Stricker PA, Zuppa AF, Fiadjoe JE, Maxwell LG, Sussman EM, Pruitt EY, Goebel TK, Gastonguay MR, Taylor JA, Bartlett SP, Schreiner MS: Population pharmacokinetics of ε-aminocaproic acid in infants undergoing craniofacial reconstruction surgery. Br J Anaesth 2013; 110:788–99
24. Harrison AM, Davis S, Eggleston S, Cunningham R, Mee RB, Bokesch PM: Serum creatinine and estimated creatinine clearance do not predict perioperatively measured creatinine clearance in neonates undergoing congenital heart surgery. Pediatr Crit Care Med 2003; 4:55–9
25. Grassin-Delyle S, Couturier R, Abe E, Alvarez JC, Devillier P, Urien S: A practical tranexamic acid dosing scheme based on population pharmacokinetics in children undergoing cardiac surgery. Anesthesiology 2013; 118:853–62

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