Pharmacokinetics of Tranexamic Acid in Neonates, Infants, and Children Undergoing Cardiac Surgery with Cardiopulmonary Bypass

Mark C. Wesley, M.D., Luis M. Pereira, Ph.D., Laurie A. Scharp, B.S., Sitaram M. Emani, M.D., Francis X. McGowan, Jr., M.D., James A. DiNardo, M.D.

ABSTRACT

Background: Tranexamic acid (TXA) is one of the most commonly used antifibrinolytic medications in children undergoing repair of congenital heart defects. However, a pharmacokinetics analysis of TXA has never been performed in neonates or young children undergoing complex cardiac surgeries using cardiopulmonary bypass, hypothermia, circulatory arrest, and ultrafiltration. A comprehensive pharmacokinetics study was performed in this patient population.

Methods: Fifty-five patients ranging from 2 days through 4 yr old were categorized into three groups: children less than 2 months old, infants 2 months to 1 yr old, and children greater than 1 yr old and weighing up to 20 kg. TXA was given as a bolus of 100 mg/kg followed by an infusion of 10 mg · kg^{-1} · h^{-1} throughout the surgery. A dose of 100 mg/kg was placed in the cardiopulmonary bypass prime. A total of 16 to 18 samples were obtained from all patients throughout surgery. Plasma TXA concentrations were measured by high-performance liquid chromatography and modeled under a nonlinear mixed-effects framework with a two-compartment structural model.

Results: Cardiopulmonary bypass had a statistically significant impact on all pharmacokinetic parameters. Age was a better covariate than body weight, affecting both the distribution and the elimination of TXA. However, weight performed well in some cases. Other covariates including body surface area, pump prime volume, ultrafiltrate volume, and body temperature did not improve the model.

Conclusions: This TXA pharmacokinetic analysis is reported for the first time in neonates and young children undergoing complex cardiac surgeries with cardiopulmonary bypass. Dosing recommendations are provided as guidance for maintaining desired target concentrations. **(Anesthesiology 2015; 122:746-58)**

TRANEXAMIC acid (TXA) is a hydrophilic molecule that reduces blood loss and transfusion requirements in children undergoing cardiac surgeries that use cardiopulmonary bypass (CPB).[1,2] A recent review of 22,258 pediatric cardiac surgical patients indicates that TXA improved outcomes, defined as reduced in-hospital mortality and bleeding requiring surgical intervention, when compared with epsilon-aminocaproic acid and aprotinin.[3]

Because comprehensive dose-response studies of TXA in pediatric cardiac surgical patients have not been performed, the most effective dosing schedule is still unknown. In a series of studies, Chauhan *et al.*[2,4] reported that TXA bolus doses of 10 mg/kg given after induction of anesthesia, on CPB, and after protamine are effective in reducing blood loss, transfusion requirements, and re-exploration for bleeding in cyanotic children across a wide age range. This dosing schedule was also found to be more effective than a loading dose of 10 mg/kg followed by an infusion of 1 mg · kg^{-1} · h^{-1}. However, bolus doses separated by a long time interval without a maintenance infusion are counterintuitive for maintaining stable

What We Already Know about This Topic

- Tranexamic acid (TXA) is an antifibrinolytic agent that reduces blood loss and transfusion requirements in children undergoing cardiac surgeries with cardiopulmonary bypass
- The safest and most effective dosing schedule in children is unknown because dose-response and pharmacokinetic studies have not been performed

What This Article Tells Us That Is New

- Tranexamic acid pharmacokinetics were determined during cardiac surgery in 55 children categorized into three age groups: less than 2 months old; 2 months to 1 yr old; and more than 1 yr old and weighing up to 20 kg
- Dosing recommendations were modeled for each age group for plasma concentrations of 20, 60, and 150 μg/ml
- The safe and effective Tranexamic acid concentration range needs to be better defined

The work has been presented at the Society of Cardiac Anesthesiologists, 17th Annual Update on Cardiopulmonary Bypass, Snowmass Village, Colorado, March 14, 2012. Preliminary findings only.

Submitted for publication January 7, 2014. Accepted for publication November 11, 2014. From the Department of Anesthesiology, Perioperative and Pain Medicine, Harvard Medical School and Boston Children's Hospital, Boston, Massachusetts (M.C.W., L.M.P., J.A.D.); Boston Children's Hospital, Boston, Massachusetts (L.A.S.); Department of Cardiac Surgery, Harvard Medical School and Boston Children's Hospital, Boston, Massachusetts (S.M.E.); and Department of Anesthesiology and Critical Care, The Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, Pennsylvania (F.X.M.).

 Anesthesiology 2015; 122:746-58

concentrations of TXA.[5,6] In an efficacy study by Reid *et al.*,[1] a TXA bolus of 100 mg/kg on induction of anesthesia followed by a continuous infusion of 10 mg · kg^{-1} · h^{-1} and a bolus of 100 mg/kg in the bypass circuit reduced blood loss by 24% when compared with saline placebo. In addition, total transfusion requirements and donor exposures were reduced.

Several attempts have been made to determine the effective plasma concentration of TXA in cardiac surgical patients, but unanimity is lacking especially across different age groups. Pharmacokinetic modeling of clinically efficacious TXA dosing in adults lead to reporting of dosing schedules needed to maintain plasma levels of 52.5 and 126 μg/ml.[7,8] However, recent studies also suggest that plasma levels up to 150 μg/ml may be more effective and safe in adults with severe bleeding.[9,10] There are multiple *in vitro* studies, which have focused on determining the TXA concentration needed to prevent fibrinolysis, inhibit platelet activation, or increase thrombin generation. Yee *et al.*[11] recently reported that TXA inhibits fibrinolysis at a plasma level of 6.54 μg/ml in neonates and 17.5 μg/ml in adults. Plasmin-induced platelet activation seems to be reduced by 50% when platelet-rich plasma is incubated with 16 μg/ml of TXA.[12] Intrinsic generation of thrombin through activation of factor XII requires high plasma concentrations of TXA and has been proposed as a mechanism of action.[9,13]

The goal of the present study was to conduct a comprehensive data-rich pharmacokinetic analysis of TXA in neonates and young children having complex cardiac surgery using our standard dosing regimen. As additional information regarding efficacy and side effects becomes available through *in vivo*, *ex vivo*, and *in vitro* plasma concentration studies, our pharmacokinetic model will allow a dosing choice that better targets appropriate TXA concentrations.

Materials and Methods

Before initiation of this study, Institutional Review Board (Boston, Massachusetts) approval was obtained, and the study was listed on Clinical Trials.org (NCT01045356). Informed consent was obtained from the parents of 55 children who ranged in age from 2 days to 4 yr 10 months old. Blood and ultrafiltrate samples were obtained from all 55 patients. In accordance with institutional practice based on the study by Reid *et al.*,[1] a 100 mg/kg bolus of TXA was given over 5 min after induction of anesthesia and before incision, followed by an infusion of 10 mg · kg^{-1} · h^{-1}, which was maintained throughout the procedure. An additional 100 mg/kg dose was added to the CPB prime before the initiation of CPB. We collected a total of 16 to 18 whole blood samples (2 ml per sample) throughout the surgery on all 55 patients. Because the CPB circuit was primed with homologous blood for all patients, the sampling schedule (table 1) was judged as acceptable by the Institutional Review Board. Circulatory arrest was not included in CPB time, and samples were not collected during circulatory arrest. To better characterize the elimination kinetics, three additional samples were obtained from five patients in each group after termination of the TXA infusion. These samples were obtained at the end of the infusion and 1 h and 3 h later in the cardiac intensive care unit. At the end of surgery, samples were collected from the ultrafiltrate and modified ultrafiltrate.

The youngest cohort (group 1) consisted of 15 patients ranging in age from 2 days to 2 months old and a weight of 2.5 to 3.8 kg. Thirteen of the 15 patients were full-term, one patient was born at 37 6/7 weeks estimated gestational age, and one patient was born at 36 weeks estimated gestational age and was 5 weeks old at the time of the surgery. The pump prime ranged from 240 to 255 ml (mean 241 ml) and included whole blood or reconstituted whole blood (one unit packed erythrocytes less than 7 days old and one unit of fresh frozen plasma combined) in all these patients. Ultrafiltration was performed in all patients throughout CPB and five had modified ultrafiltration (MUF). Hypothermia was used in all patients and ranged from 17.4 to 28.3°C. CPB time ranged from 79 to 222 min. Circulatory arrest was used in eight of these patients. Two received an extra TXA bolus of 100 mg/kg after termination of CPB at the request of the surgeon. All doses and times of administration were included in the analysis of the resulting concentrations.

The infant group (group 2) consisted of 20 patients ranging from 2 months and 9 days to 11 months and 18 days old weighing from 3.5 to 7.6 kg. Six patients had a previous sternotomy. The pump prime volume ranged from 240 to 255 ml (mean 241 ml) and included fresh whole blood or reconstituted whole blood in all the patients. All patients had ultrafiltration throughout CPB and four had MUF. Hypothermia ranging from 22.8° to 32.6°C was used in all but one patient. CPB time ranged from 43 to 246 min.

Group 3 consisted of 20 patients ranging from 12 months to 4 yr 10 months old and a weight of 7.7 to 18 kg. Sixteen patients had a previous sternotomy. The CPB prime volume ranged from 240 to 590 ml (mean 440 ml) and fresh whole blood or reconstituted whole blood was included in all but two of the patients. All patients had ultrafiltration and none had MUF. Hypothermia ranging from 26.4 to 33°C was used in all but one patient. CPB time ranged from 26 to 259 min. No patients in this group underwent circulatory arrest. See table 2 for a summary of demographic data and clinical parameters for all three groups.

Anesthesia Technique and CPB Management

The anesthetic technique used included midazolam, high-dose fentanyl, neuromuscular blockade, and inhaled agent as tolerated. No patients received propofol as a primary anesthetic. However, six of the patients were started on low-dose propofol infusions at the end of surgery in preparation for transport to the cardiac intensive care unit.

Table 1. TXA Sample Collection Schedule

Time	Label	TXA Dosing	Blood Drawing
T1	Postinduction	—	Baseline
T2	Loading bolus	100 mg/kg/5 min	At the end of the bolus
T3	Maintenance infusion	10 mg · kg^{-1} · h^{-1}	At 2 min postbolus
T4			At 4 min postbolus
T5			At 6 min postbolus
T6			At 10 min postbolus
T7			At 20 min postbolus
T8	CPB start (pump preloaded with TXA)	100 mg/kg in CPB circuit (continued 10 mg · kg^{-1} · h^{-1} infusion)	Immediately after CPB start
T9			At 2 min on CPB
T10			At 4 min on CPB
T11			At 6 min on CPB
T12			At 10 min on CPB
T13			At 20 min on CPB
T14			At 30 min on CPB
T15			At 40 min on CPB
T16			At 60 min on CPB
T 17	CPB end		At 30 min post-CPB
T 18	—		At 60 min post-CPB
T19	—	Infusion stopped	At the end of TXA infusion
T20	—	—	At 1 h postinfusion
T21	—	—	At 3 h postinfusion

CPB = cardiopulmonary bypass; TXA = tranexamic acid.

Table 2. Demographic and Clinical Parameters

	Mean or No.	Median	Minimum	Maximum
Patients	55	—	—	—
Age (months)	14.4	5.0	0.05	58
Length (cm)	69	63	41	108
Male/female	29/26	—	—	—
Body weight (kg)	7.5	6.6	2.5	18
BSA (m^2)	0.44	0.33	0.18	4.2
Lowest CPB temperature (°C)	27.5	28.1	17.4	34
First operation/redo	32/23	—	—	—
Duration of CPB (h)	2.5	2.4	0.43	4.3
Duration of TXA maintenance infusion (h)	5.0	5.0	1.4	8.8
EBV(ml)	626	562	213	1,440
Prime volume (ml)	313	240	240	590
Crystalloid prime vol. (ml)	76	40	10	590
Total crystalloid vol. (ml)	304	235	0	1,205
Blood prime vol. (ml)	233	220	0	454
Total erythrocytes (ml)	74	12	0	309
Urine output (ml)	160	90	6	880
Creatinine day 1 (g/dl)	0.34	0.3	0.1	0.8
Creatinine day 2 (g/dl)	0.36	0.3	0.2	0.8

BSA = body surface area; CPB = cardiopulmonary bypass; EBV = estimated blood volume; TXA = tranexamic acid.

The CPB circuit in the youngest children had a prime volume of 240 ml. This included a Terumo (Terumo Europe, Bagshot Surrey, United Kingdom) FX05 oxygenator (43 ml) and reservoir (100 ml). The arterial line prime volume was 30 ml, the venous line was 52 ml, and the boot was 3/16 inch diameter and required 15 ml. Group 2 had the same components, except the boot is 1/4 inch diameter and required 30 ml resulting in a prime volume of 255 ml. In group 3, a Terumo FX15-30 oxygenator (144 ml) and reservoir (175 ml) were combined with an arterial line, which required 75 ml and the venous line required 140 ml. The boot was 3/8 inch diameter and required 65 ml resulting in a 590-ml pump prime. The pump prime volumes do not include the cardioplegia volume or the hemoconcentrator volume of 35 ml. CPB flow rates were adjusted for hypothermia. The following guidelines were used for minimal

CPB flow ($l \cdot min^{-1} \cdot m^{-2}$) at different temperatures: 2.2 at 32°C; 1.8 at 28°C; 1.4 at 24°C; and 0.8 at 18°C. In general, the flow rates were maintained higher than these levels. We use nonpulsatile CPB. Continuous ultrafiltration and MUF were performed to effectuate hemoconcentration, and zero balance ultrafiltration was not performed. Therefore, no additional fluid was added to the CPB circuit in conjunction with ultrafiltration. Cell saver was not used.

Sample Preparation

Whole blood samples were drawn into EDTA vacutainer tubes and immediately placed on ice. The plasma was then separated by centrifugation at 1,000*g* for 10 min and stored at –80°C as previously reported by Goobie *et al.*[14] For high-performance liquid chromatography analysis, the samples were thawed in small batches and 100 μl of the internal standard (1 mM L-norleucine in 0.1N HCL) was added to an equal volume of plasma, which was then vortexed for 30 s. This mixture was then purified using Amicon Ultracel 10K ultracentrifugal filter cartridges per the manufacturer's instructions (Millipore, Billerica, MA). After centrifugation at 6,500 revolutions per minute for 30 min, 50 μl of Amicon membrane filtrate were dried under vacuum and then treated with 10 μl of a solution containing 1 M sodium acetate: tetraethylammonium: methanol (2:2:1, v/v/v). These solutions were again vacuum-dried and derivatized with the addition of 20 μl methanol:tetraethylammonium :water:phenyl isothiocyanate (7:1:1:1, v/v/v/v) for 20 min at room temperature. Derivatized samples were vacuum-dried, reconstituted in 100 μl solution containing 5 mM sodium phosphate at pH 7.4 and acetonitrile (950:50, v:v), and transferred to amber glass vials for high-performance liquid chromatography injection.

TXA Quantification

TXA standard was obtained from Pharmacia/Upjohn, division of Pfizer Inc. (New York, NY). The internal standard L-norleucine, the derivatization agent phenyl isothiocyanate, and all other reagents were purchased from Sigma-Aldrich (St. Louis, MO) in high-performance liquid chromatography grade or better. High-performance liquid chromatography analysis was conducted on an Agilent 1200 system (Agilent Co., Santa Clara, CA) consisting of a quaternary pump, an autosampler, an in-line degasser, and a diode array ultraviolet/visible detector. The analytical column was a Nova-Pak reverse phase C18 (4 μm; 3.9 × 300 mm; Waters Corp., Milford, MA) used in conjunction with a freshly degassed mobile phase that consisted of two components. Component A had 70 mM sodium acetate (pH6.5) and acetonitrile (975:25, v:v), while component B contained acetonitrile:water:methanol (450:400:150, v:v/v). A gradient mixture of components A and B was used as: 0 min 3% B, 13.5 min 9% B, 20 min 30% B, 35 min 100% B, 52 min 3% B. The mobile phase flow was 1 ml/min, column temperature was 38°C, injection volume was 10 μl, and detection carried out at 254 nm wavelength. The system was controlled by the ChemStation software, including the processing and integration of the chromatograms. Standard calibration curves of TXA/internal standard peak areas ratio *versus* TXA concentrations were repeated daily and were linear and homoscedastic over a range of 10 to 1,800 μg/ml of TXA with correlations above 0.99. Quality control samples were prepared by regularly and randomly spiking individual unknowns with 500 μg/ml of standard TXA and occasionally 1,000 μg/ml. Intra- and interday variability was 5.1% and 7.8%, while intra- and interday accuracy was 97% and 93%, respectively. The lower limit of quantification was 10 μg/ml, and the limit of detection was 3 μg/ml.

Pharmacokinetic Modeling

Pharmacokinetic analyses were conducted by nonlinear mixed-effects modeling using the software packages Monolix 4.1.2 (Lixoft, Orsay, France) and NONMEM 7.2 (Icon Development Solutions, Ellicott City, MD) with the Intel Visual Fortran compiler professional edition version 11.1 (Intel Co., Santa Clara, CA) and the Microsoft Visual Studio 2008 shell and libraries (Microsoft Co., Redmond, WA) installed. The PLT Tools package (PLTSoft, San Francisco, CA) was also used as a front end for NONMEM to produce diagnostics plots and facilitate the model building process, using the MatLab2009 extension (MathWorks Inc., Natick, MA) and R version 2.12.*

Structural Model

One, two, and three compartment models were compared based on their goodness of fit to individual and naive pooled data, as well as on the respective Akaike information criterion and Bayesian information criterion. The two-compartment model with first-order central elimination was found to best characterize the disposition of TXA, consistent with previous investigations.[8,15] For a constant rate, infusion systemic plasma drug concentrations before the end of infusion at T_{inf} are described as,

$$C(t) = C_{SS}\left(1 - \frac{k_{10}-\beta}{\alpha-\beta}e^{-\alpha t} - \frac{\alpha-k_{10}}{\alpha-\beta}e^{-\beta t}\right), \text{ for } t \le T_{inf} \quad (1)$$

and postinfusion as,

$$C(t) = C(T_{inf})\left(\frac{k_{10}-\beta}{\alpha-\beta}e^{-\alpha(t-T_{inf})} - \frac{\alpha-k_{10}}{\alpha-\beta}e^{-\beta(t-T_{inf})}\right), \quad \text{for } t > T_{inf} \quad (2)$$

being the steady-state concentration

$$C_{SS} = \frac{R_0}{k_{10}V_1} \quad (3)$$

* Cran.R-project.org. Accessed November 11, 2014.

with R_0 as the rate of infusion, V_1 the apparent volume of distribution for the central compartment, and k_{10} the elimination rate constant from the central compartment.

At the time of transition from the loading to the maintenance infusion, that is, at 5 min in this study, the subsequent TXA concentrations result from the superposition of equation 2 with R_{01} equal to the loading rate (100 mg/kg per 5 min), and equation 1 starting at that time with R_{02} equal to the maintenance rate (10 $mg \cdot kg^{-1} \cdot h^{-1}$), assuming linearity and superposition. A clearance-based parameterization was also used for computational reasons, with systemic clearance CL (= $k_{10} \times V_1$), intercompartmental clearance Q (= $k_{12} \times V_1$ = $k_{21} \times V_2$), volume of distribution of the peripheral compartment V_2, and mass transfer first-order rate constants k_{12} and k_{21} between central and the peripheral (1 and 2) compartments, respectively. Secondary parameters such as the elimination half-life ($T_{1/2,elim} = \ln(2)/\beta$) and the steady-state volume of distribution ($V_{SS} = V_1 + V_2$) were also calculated.

Population Model

The initial fixed effects checking tool in Monolix was used to screen across individual fits. An exploratory two-stage analysis was then conducted to determine initial estimates for the typical pharmacokinetic parameters. Basic competing models were coded in MLXTRAN script using a differential equations parameterization. Given the two-compartment structural model chosen, the subroutines ADVAN3 and TRANS4 were also used in NONMEM. Four parameters were defined as fixed effects, that is, systemic clearance (CL), apparent volume of distribution for the central (V_1), and peripheral (V_2) compartments, and intercompartmental clearance (Q). The impact of the CPB was modeled with a binary indicator variable that took the value of one during CPB and zero otherwise. This flagging switched the first set of adjustable parameters to a second set independently estimated as CL_{CPB}, $V_{1,CPB}$, Q_{CPB}, and $V_{2,CPB}$. The random effects modeled the between-subjects variability, that is, the biological variability affecting each fixed parameter. For all typical values of the pharmacokinetic parameters (TVPK), this variance model followed a log-normal distribution according to,

$$\ln\left(PK_{ij}\right) = \ln\left(TVPK_j\right) + \eta_{ij} \quad (6)$$

where PK_{ij} is the jth parameter for individual i, $TVPK_j$ is the population typical value for the corresponding jth parameter (*e.g.*, clearance), and η_{ij} is the intersubject variability. Each η_{ij} was assumed to be a normal random variable with mean zero and variance ω^2. Within-subjects variability was captured by a proportional residual error model according to,

$$C_{ik} = \hat{C}_{ik} \times (1 + \varepsilon_{ik}) \quad (7)$$

where C_{ik} is the kth measured concentration for individual i, $\hat{C}_{ik}$ is the corresponding predicted concentration, and ε_{ik} is a random variable normally distributed with mean equal to zero. Additive and combined error models were tried and found not better.

In NONMEM, all models were optimized using the first-order conditional estimation method with the interaction option. In Monolix, the stochastic approximation expectation maximization algorithm was used with a single Monte Carlo Markov chain and simulated annealing optimization. Population and empirical Bayesian estimates of the individual pharmacokinetic parameters were obtained for each subject by *post hoc* estimation after minimizing the Bayesian objective function. Upon convergence, the Fisher information matrix and the likelihood function were calculated.

Model Selection

Possible covariates, such as body weight and age, were plotted against the pharmacokinetic parameters across the population seeking for relevant correlations. The likelihood ratio test was used for this model building process. The influence of each covariate on the base model was first assessed by forward stepwise inclusion. Their leverage in lowering the objective function value was tested for significance. A drop of objective function value per each additional parameter of at least 3.84 points, or 5.99 for two parameters at once (following a chi-squared distribution with $\alpha = 0.05$ and df = 1 or 2, respectively), was chosen as the criterion to include it/them in the model. Each covariate, for example the patient's age (AGE), was thus tested by entering it in the model (*e.g.*, for CL_i = clearance of individual i) as follows,

$$\ln\left(CL_i\right) = \ln\left(TVCL\right) + \theta_{CL,AGE} \times AGE_i + \eta_i \quad (8)$$

where TVCL is the typical population clearance, and $\theta_{CL,AGE}$ is the coefficient of its dependence on AGE. Competing covariate models were assessed by backward deletion, meaning removing covariates one at a time to confirm their significance. For this, a level of α less than equal to 0.005 was chosen such that a chi-square value of Δ objective function value greater than 7.88 was required per one degree of freedom, that is, one covariate removed. Models were also screened for the lowest Akaike information criteria and Bayesian information criteria, as well as for the corresponding visual predictive checks. The final model was validated by bootstrapping the fixed parameters and comparing the concentrations resulting from the bootstrapped samples with the original data.

Results

A total of 889 concentration-time observations were obtained from the 55 studied patients. These were first analyzed all together and then grouped by age in group 1 with 15 patients from 0 to 2 months (mean = 0.55 months), group 2 with 20 patients from 2 to 12 months (mean = 5.8 months), and group 3 with 20 patients from 12 to 58 months (mean = 36 months). TXA concentrations for all patients averaged 444.4

μg/ml (min = 111.0 μg/ml; max = 1,644.0 μg/ml) between the loading dose and the onset of CPB and 433.9 μg/ml during CPB (min = 110.3 μg/ml; max = 1,804.7 μg/ml). Figure 1, A–C summarizes the pooled TXA concentrations for the three age groups, while figure 2 depicts the individual concentrations and profiles of 12 typical subjects.

As shown in figure 3, A and B, the final population model provided a good *post hoc* individual prediction of the TXA concentrations with a substantial reduction in variability. The trendline across all observations closely follows the 45° identity line, revealing no systematic under- or overprediction.

The final model was used to simulate Monte Carlo replicates to construct a visual predictive check with adjustable bins and the Uppsala prediction correction. As shown in figure 4, the empirical and theoretical TXA concentration modes are in good agreement, and 90% prediction intervals on the 10th, 50th, and 90th percentiles revealed no significant outliers.

The heteroscedasticity in the data was handled by a proportional residual error model. Individually weighted residuals plotted *versus* time and *versus* predicted TXA concentrations were mostly contained within the ±2 interval (figure 5). All residuals had empirical distributions and histograms normal and centered on zero. Normalized prediction distribution errors were calculated and revealed the same behavior.

A total of 500 replicate data sets were generated from the original one by random sampling with replacement, that is, bootstrapping. Estimates of the parameters in the final model were obtained from each set with which empirical 95% confidence intervals were calculated. As shown in table 3, these were in very good agreement with the original estimates which all fell between the 2.5th and the 97.5th percentile. Table 4 is a summary of the model building process including the significance of the relevant covariate coefficients.

Notably, age centered on the cohort median (*i.e.*, 5 months) was the most relevant covariate. Body weight had a similar leverage on systemic clearance and central volume of distribution, either centered on the median or normalized to 70 kg with a fixed 0.75 allometric coefficient. However, body weight scaling introduced individual bias away from the median on extrapolation toward the very young patients. As a consequence, age was preferred for our simulations. Other covariates such as body surface area, pump prime volume, ultrafiltrate volume, and body temperature did not enhance the model (table 3). Table 4 summarizes the final model parameters used for the simulation of other dosing schemes.

Despite the parameterization, the influence of the CPB on all pharmacokinetic parameters was statistically significant. Both the distribution and the elimination of TXA were affected by the age. As summarized in table 5, during CPB the volume of distribution and the systemic clearance are increased. Similar findings were also previously reported with epsilon-aminocaproic acid.[16]

Because the plasma concentration of TXA necessary to provide optimal antifibrinolytic and anti-inflammatory effects in children is unknown, and given that seizures and thrombosis have been associated with the use of TXA, we modeled dosing recommendations for three typical plasma levels 20, 60, and 150 μg/ml. The high and low concentrations are based on two recent pharmacokinetic studies by

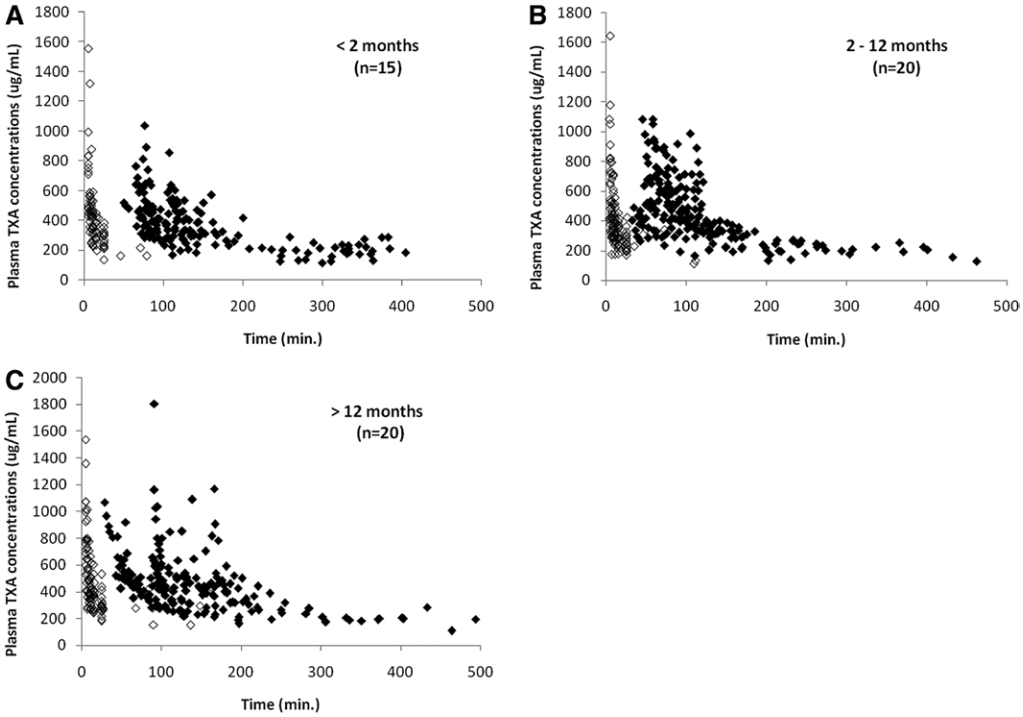

Fig. 1. (*A, B, C*) Tranexamic acid (TXA) plasma concentrations by age group. *Open diamond*—before cardiopulmonary bypass (CPB); *closed diamond*—during CPB.

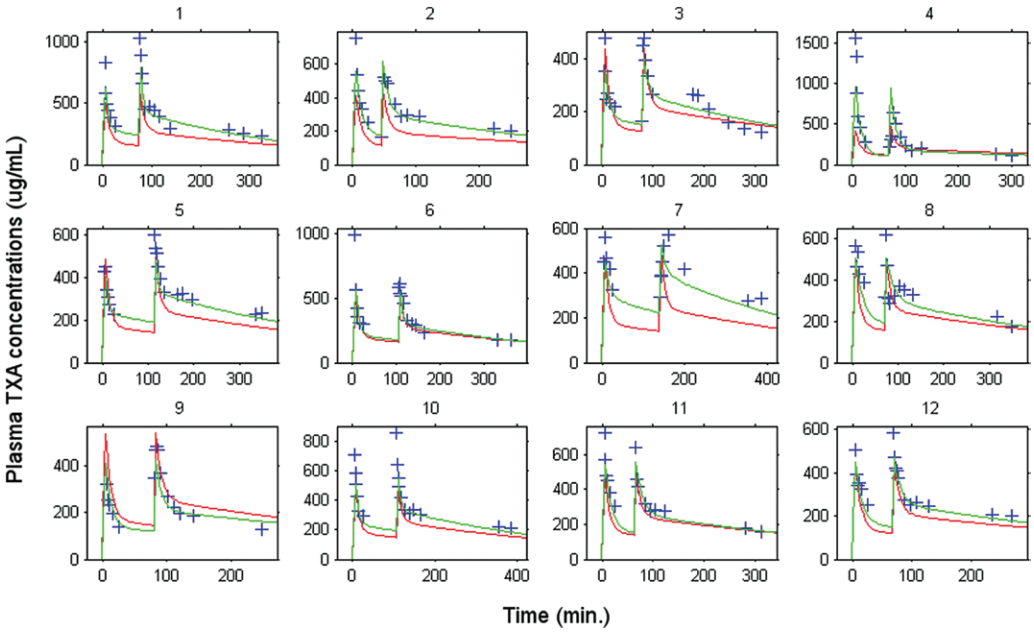

Fig. 2. Typical individual (*green*) and population (*red*) curve fits for the first 12 of 55 patients. TXA = tranexamic acid.

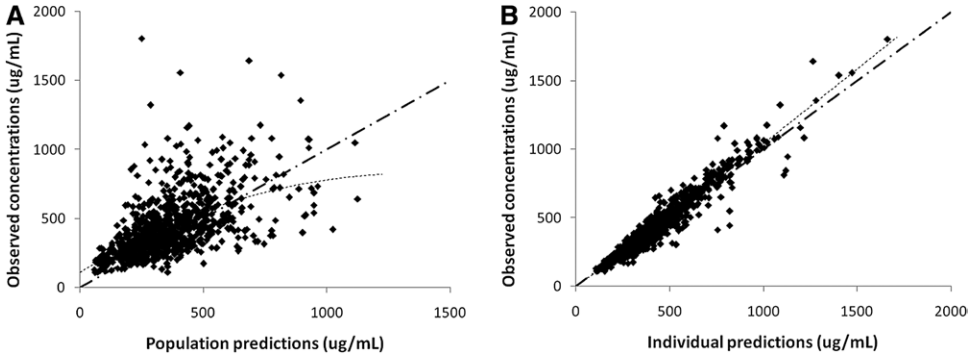

Fig. 3. Observed *versus* population (*A*) and individually (*B*) predicted tranexamic acid (TXA) plasma concentrations (*dashed line* is the moving average trendline; *dash-dotted line* is the identity line).

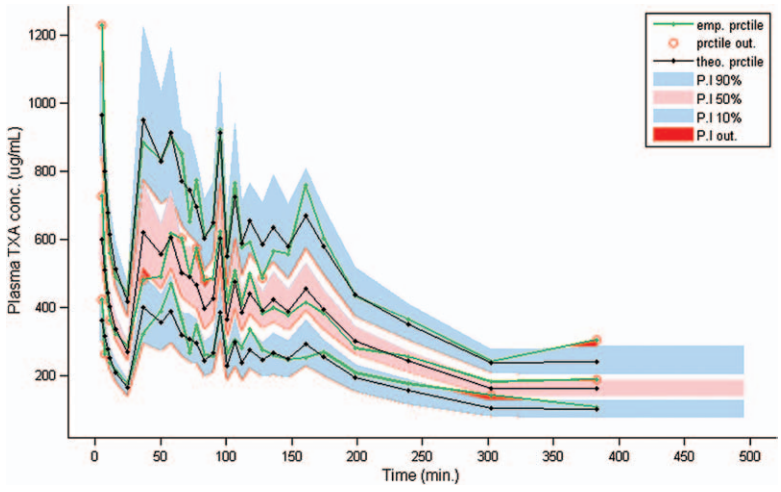

Fig. 4. Visual predictive check for the final model with 90% prediction intervals (P.I.) around the 10th, 50th, and 90th percentile. TXA = tranexamic acid.

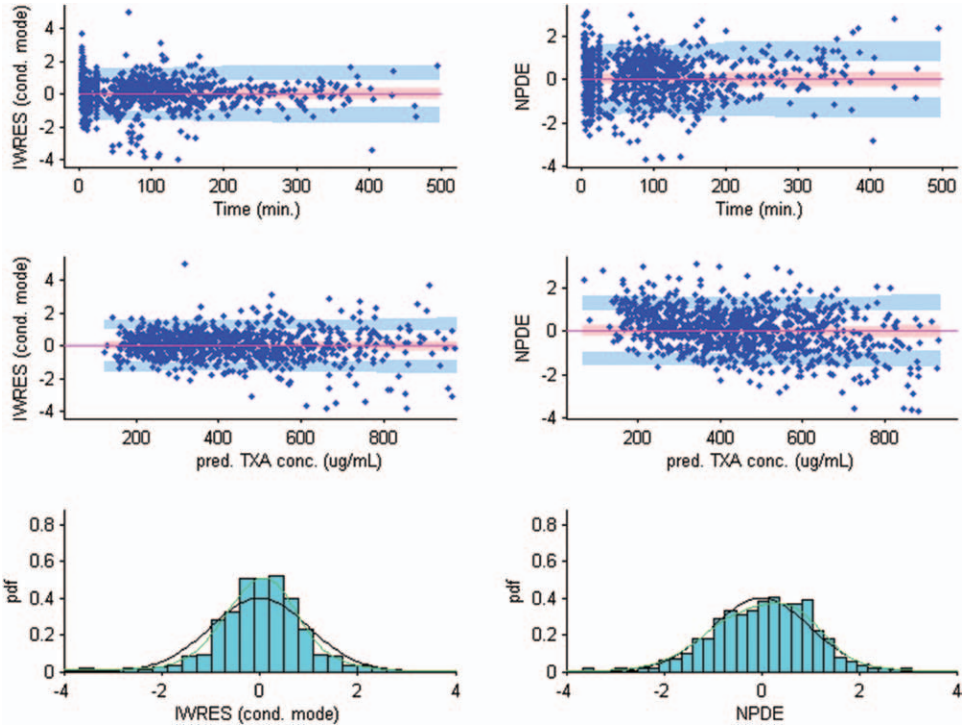

Fig. 5. Individually weighted (IWRES) and normalized prediction distribution errors (NPDE) plotted *versus* time and tranexamic acid (TXA) concentrations.

Table 3. Final Population Parameters

Parameter	Estimate (%RSE)	Bootstrap Median (95% CI)	IIV (%RSE)
CL (l · min^{-1} · kg^{-1}) = θ_1.(Age/5)$^{\theta 2}$	θ_1 = 0.0130 (36)	0.0126 (0.0119–0.0133)	3.45 (12)
	θ_2 = 0.0210 (21)	0.0231 (0.0186–0.0242)	
CL_{CPB} (l · min^{-1} · kg^{-1}) = θ_9.(Age/5)$^{\theta 10}$	θ_9 = 0.0165 (6)	0.0154 (0.0133–0.0171)	0.337 (12)
	θ_{10} = 0.0306 (10)	0.0289 (0.0275–0.0314)	
V_1 (l/kg) = θ_3.(Age/5)$^{\theta 4}$	θ_3 = 0.0440 (8)	0.0462 (0.0423–0.0477)	0.442 (12)
	θ_4 = 0.0254 (15)	0.0257 (0.0237–0.0268)	
$V_{1,CPB}$ (l/kg) = θ_{11}.(Age/5)$^{\theta 12}$	θ_{11} = 0.258 (11)	0.251 (0.243–0.267)	0.643 (12)
	θ_{12} = 0.0300 (18)	0.0292 (0.0278–0.0306)	
V_2 (l/kg) = θ_5.(Age/5)$^{\theta 6}$	θ_5 = 1.26 (7)	1.18 (1.03–1.29)	0.359 (16)
	θ_6 = 0.0256 (12)	0.0264 (0.0243–0.0272)	
$V_{2,CPB}$ (l/kg) = θ_{13}.(Age/5)$^{\theta 14}$	θ_{13} = 2.84 (12)	2.96 (2.55–3.14)	0.675 (12)
	θ_{14} = 0.0196 (28)	0.0194 (0.0188–0.0213)	
Q (l · min^{-1} · kg^{-1}) = θ_7.(Age/5)$^{\theta 8}$	θ_7 = 0.112 (12)	0.118 (0.102–0.127)	0.688 (12)
	θ_8 = 0.0252 (23)	0.0244 (0.0216–0.0263)	
Q_{CPB} (l · min^{-1} · kg^{-1}) = θ_{15}.(Age/5)$^{\theta 16}$	θ_{15} = 0.183 (43)	0.178 (0.166–0.198)	2.40 (13)
	θ_{16} = 0.0438 (48)	0.0451 (0.0437–0.0463)	
Proportional residual variability	—	—	0.153 (3)

CI = confidence interval; CPB = cardiopulmonary bypass; IIV = interindividual variability; %RSE = percent relative standard error.

Grassin-Delyle *et al.*,[9,17] and the intermediate concentration is similar to the middle target identified by Dowd *et al.*[8] Table 6 summarizes typical dosing schedules that will achieve these plasma concentrations in young children.

Simulated target serum concentrations for each age group using the three recommended dosing schedules are shown in figure 6, A–C. These simulations are all based on the bolus dose given over 15 min, initiation of CPB at 50 min after the bolus is complete, and ending CPB within 360 min of the start of the bolus. For these simulations, the pump prime volume was fixed at 240 ml for groups 1 and 2 and at 440 ml for group 3, based on the mean values extracted from each patient's cohort. The pump prime dose is calculated by multiplying the desired concentration (20, 60, or 150 μg/ml) by the prime volume in milliliters.

Table 4. Model Building Summary (Not Exhaustive)

Model	Parameterization	–2LL	AIC	BIC	*P* Value
1	CL,V_1,Q,V_2	13,282	13,314	13,346	—
2	$1 + CL_{CPB},V_{1,CPB},Q_{CPB},V_{2,CPB}$	11,115	11,149	11,183	—
3	$2 + \theta_{CL}.(BW/7)^{\theta'CL}+\theta_{CLCPB}.(BW/7)^{\theta'CLCPB}$	11,098	11,133	11,168	0.011
4	$2 + \theta_{CL}.(BW/70)^{0.75}+\theta_{CLCPB}.(BW/70)^{0.75}$	11,096	11,129	11,162	0.024
5	$2 + \theta_{CL}.(Age/5)^{\theta'CL}$	11,033	11,065	11,097	2.6×10^{-6}
6	$3 + \theta_{V1}.(BW/7)^{\theta'V1}+\theta_{V1CPB}.(BW/7)^{\theta'V1CPB}$	11,054	11,091	11,128	4.7×10^{-4}
7	$3 + \theta_{V1}.(BW/70)+\theta_{V1CPB}.(BW/70)$	11,095	11,133	11,171	7.6×10^{-3}
8	$5 + \theta_{CL,CPB}.(Age/5)^{\theta'CL,CPB}$	11,060	11,096	11,132	$<1.0^{-10}$
9	$8 + \theta_{V1}.(Age/5)^{\theta'V1}+ \theta_{V1,CPB}.(Age/5)^{\theta'V1,CPB}$	11,016	11,054	11,092	7.4×10^{-8}
10	$9 + \theta_{CL}.(BSA/0.3)^{\theta'CL}$	11,099	11,132	11,165	0.26
11	$9 + \theta_{CL}.(Gender)^{\theta'CL}$	11,105	11,140	11,175	0.41
12	$9 + \theta_{CL}.(UF)^{\theta'CL}+\theta_{CLCPB}.(UF)^{\theta'CLCPB}$	11,089	11,121	11,153	0.13
13	$12 + \theta_{V1}.(UF)^{\theta'V1}+\theta_{V1}.(UF)^{\theta'V1CPB}$	11,087	11,123	11,159	0.09
14	$9 + \theta_{CL}.(Temp)^{\theta'CL}+\theta_{CLCPB}.(Temp)^{\theta'CLCPB}$	11,091	11,125	11,159	0.38
15	$9 + \theta_{V2}.(Age/5)^{\theta'V2}$	10,926	10,968	11,010	$<1.0^{-10}$
16	$15+ \theta_{V2,CPB}.(Age/5)^{\theta'V2,CPB}$	10,889	10,937	10,985	3.4×10^{-4}
17	$16+ \theta_{Q}.(Age/5)^{\theta'Q}$	10,861	10,913	10,965	2.9×10^{-4}
18	$17+ \theta_{Q,CPB}.(Age/5)^{\theta'Q,CPB}$	10,849	10,903	10,957	0.013

–2LL = minus two times the log likelihood; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; BSA = body surface area; BW = body weight; CPB = cardiopulmonary bypass; UF = ultrafiltrate volume.

Table 5. Mean Clinical PK Parameters per Age Group

Parameter	Group 1 (Mean 3.2 kg; 0.56 months)	Group 2 (Mean 6.4 kg; 5.5 months)	Group 3 (Mean 12.3 kg; 36 months)	Grassin-Delyle *et al.*[17] (5–40 kg)	Grassin-Delyle[9] (70 kg Adult)	Dowd *et al.*[8] (80 kg Adult)	Ririe[16] (εACA; Pediatric 12 kg)*
CL (l/min)	0.0396	0.0836	0.167	0.006–0.027†	0.08†	0.15	0.0408
CL_{CPB} (l/min)	0.0491	0.106	0.214	—	—	0.11	0.0252
V_1 (l)	0.132	0.284	0.568	1.0–8.0	6.6‡	10.3	2.86
$V_{1,CPB}$ (l)	0.772	1.66	3.36	—	—	11.9	2.00
V_2 (l)	3.80	8.10	16.3	2.3–18.7	10.8§	8.5	2.76
$V_{2,CPB}$ (l)	8.68	18.3	36.2	—	—	9.8	4.32
Q (l/min)	0.338	0.720	1.45	0.013–0.063†	0.537†	0.18	0.0648
Q_{CPB} (l/min)	0.530	1.18	2.45	—‖	—	0.21	0.0996
T1/2 (h)	2.19	2.09	1.19	8.4–14.1	2.7	0.82#	1.66
$T1/2_{CPB}$(h)	2.55	2.29	1.03	—	—	1.28#	3.55

*Parameters for epsilon-aminocaproic acid (not tranexamic acid). †Original units l/h (table 5). ‡ From table 3 (33.2 l in table 4). §Same in tables 3 and 4. ‖No CPB effect for 500 ml prime volume. #$Ln2/k_{10}$.

CL = systemic clearance; CPB = cardiopulmonary bypass; εACA = epsilon-aminocaproic acid; PK = pharmacokinetics; Q = distribution clearance; T1/2 = elimination half-life; V_1 = central volume of distribution; V_2 = peripheral volume of distribution.

Our model was also used to simulate concentrations for each of the three groups using the bolus-only dosing schedule suggested by Chauhan *et al.*[4] The minimum desired concentration of 20 μg/ml is not consistently maintained in any of our age groups (figure 7, A–C) due to the lack of a maintenance dosage. This pattern is even more significant when aiming at higher target concentrations.

Discussion

This is the first population pharmacokinetic analysis of TXA in neonates and young infants undergoing cardiac surgery and the only one in children having cardiac surgery where the routine clinical practices of hypothermia, deep hypothermic circulatory arrest, continuous ultrafiltration, and MUF were used. The most significant finding of this analysis is the need for different and generally reduced dosing regimens from those that are commonly used. Additional finding include the importance of developmental changes during the first year of life leading to very different dosing requirements in newborns when compared with children over 12 months old. Furthermore, individualization of the TXA dose for children between 2 and 12 months of age is necessary because unlike children younger than 2 months and those older than 12 months a single dose is not applicable.

The TXA dose predictions from our model for children greater than 12 months of age are remarkably consistent

Table 6. Dosing Recommendations Based on Minimum Desired Plasma Concentration to Be Maintained throughout the Surgery

	Low	Intermediate	High
Age	20 μg/ml	60 μg/ml	150 μg/ml
0–2 months			
Loading dose (mg/kg)	15	50	120
Infusion (mg · kg^{-1} · h^{-1})	2.5	7	17
CPB prime dose	20 μg per ml of prime volume	60 μg per ml of prime volume	150 μg per ml of prime volume
2–12 months			
Loading dose (mg/kg)	9 (6–12)	26 (20–30)	65 (45–85)
Infusion (mg · kg^{-1} · h^{-1})	2	6	14
CPB prime dose	20 μg per ml of prime volume	60 μg per ml of prime volume	150 μg per ml of prime volume
>12 months and ≤20 kg			
Loading dose (mg/kg)	4	13	31
Infusion (mg · kg^{-1} · h^{-1})	2	5.5	14
CPB prime dose	20 μg per ml of prime volume	60 μg per ml of prime volume	150 μg per ml of prime volume

Loading bolus administered over 15 min with ranges in parenthesis for the middle group.
CPB = cardiopulmonary bypass.

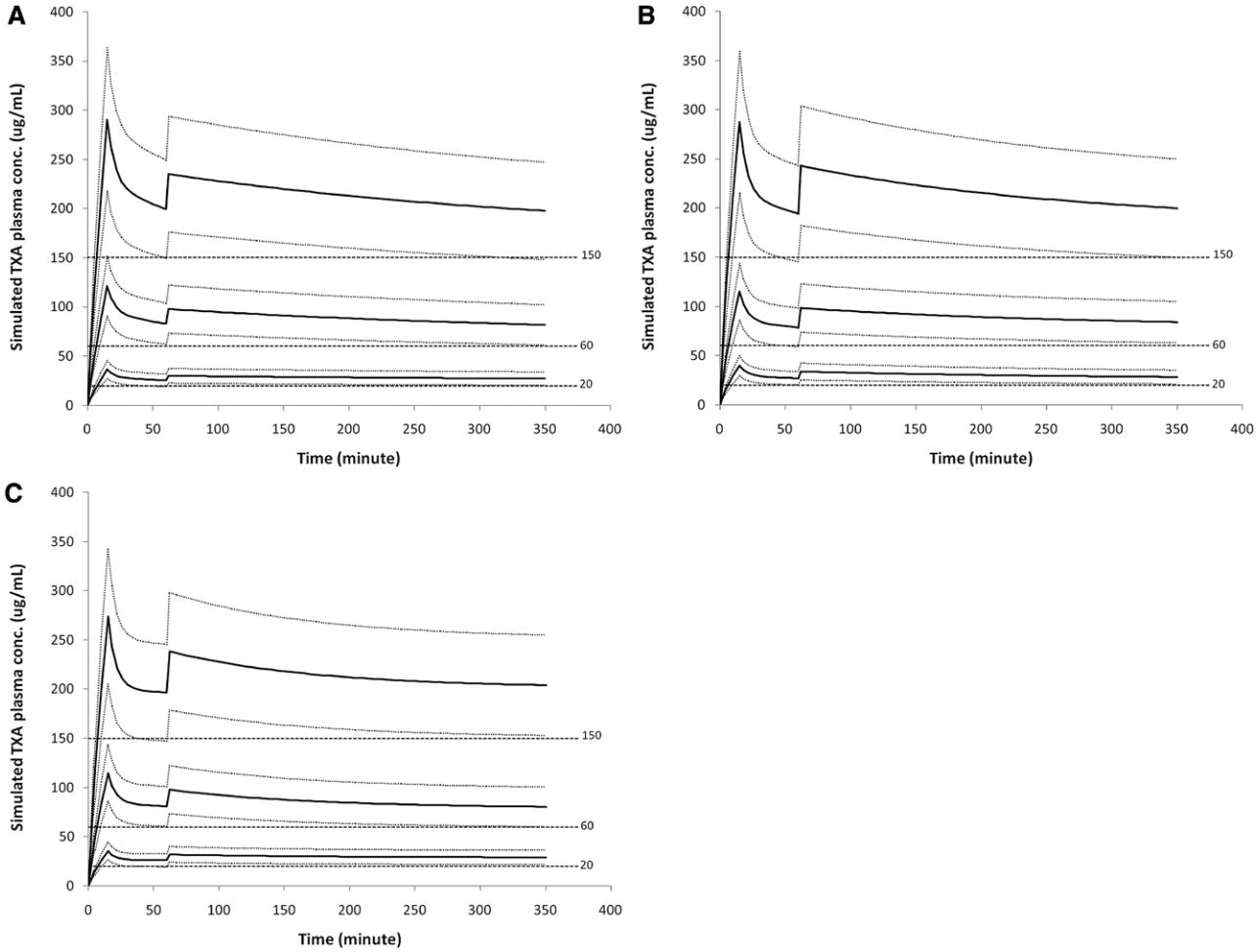

Fig. 6. (*A, B, C*) Simulations of bolus and infusion rates required to maintain 20, 60, and 150 μg/ml in *A* (the youngest group), *B* (children 2–12 months old), and *C* (children older than 1 yr and weighing up to 20 kg) according to table 6. The three mean curves (*solid lines*) are shown with corresponding upper and lower 95% CI (*dashed lines*). TXA = tranexamic acid.

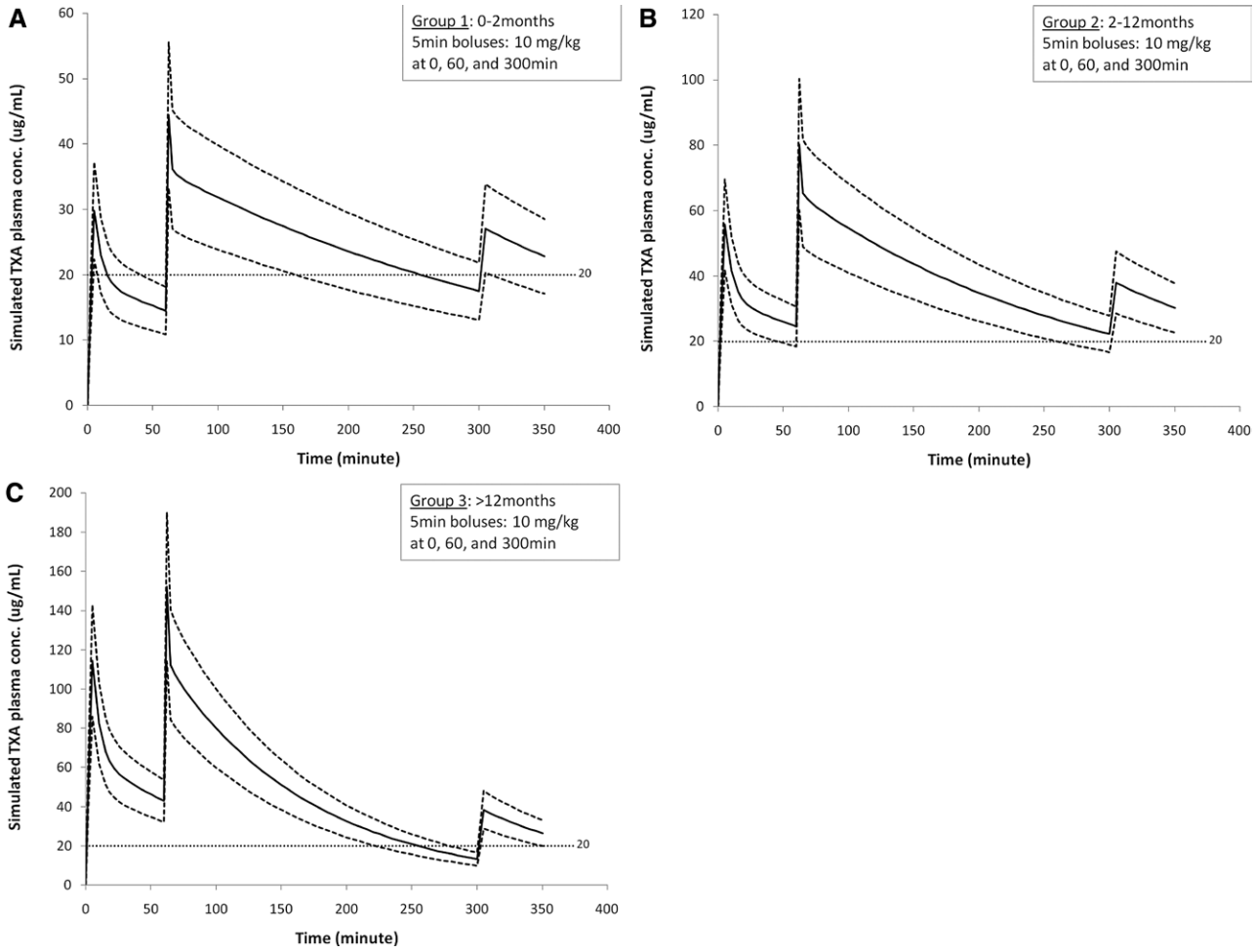

Fig. 7. (*A, B, C*) Simulations of three 10 mg/kg tranexamic acid (TXA) bolus doses given at induction, on cardiopulmonary bypass, and after protamine for our three age groups.

with those reported in children by Grassin-Delyle *et al.*[17] and in adults as reported by Dowd *et al.*[8] Based on a target serum concentration of 20 μg/ml, our recommended dosing regimen for this age group is 4 mg/kg loading dose, 2 mg · kg^{-1} · h^{-1} infusion, and a pump prime loading dose of 20 μg/ml of prime volume (table 6). For patients weighing between 5 and 40 kg with an age range of 12 months to 12 yr old, Grassin-Delyle *et al.*[17] recommended a loading dose of 6.4 mg/kg followed by an infusion of 3.1 to 2.0 mg · kg^{-1} · h^{-1} with no bolus in the pump prime. Our use of a pump prime bolus likely accounts for the slightly smaller loading dose and infusion rate (2 mg · kg^{-1} · h^{-1}) predicted by our model.

Again in children over 12 months old, very similar dosing schedules are also recommended to maintain high concentrations of TXA in all three studies. Using our model to maintain a level of 150 μg/ml, the recommended dosing schedule is a loading dose of 31 mg/kg followed by an infusion of 14 mg · kg^{-1} · h^{-1} and a pump prime of 150 μg/ml of prime volume. To maintain a level of 120 μg/ml, the Grassin-Delyle *et al.*[17] model recommends a bolus dose of 38.4 mg/kg followed by an infusion of 12 mg · kg^{-1} · h^{-1} and no pump prime. In adults, to maintain a concentration of 126 μg/ml, Dowd *et al.*[8] recommended a bolus dose of 30 mg/kg followed by an infusion of 16 mg · kg^{-1} · h^{-1} and a pump prime of 2 mg/kg.

The notable similarity of the predictions from our model and the model by Grassin-Delyle *et al.*[17] suggests that both age and allometrically scaled body weight are robust covariates, despite the significant limitation in both studies of not validating the clinical efficacy of the simulated dosing recommendations in patient cohorts. However, our findings suggest that for the very young patients, not yet studied by anybody else, developmental characteristics are better captured by age. We found that scaling body weight to an adult 70-kg value and inputting a fixed 0.75 power exponent for the clearance were not fully supported by the data. Our model and a recent report by Bjorkman *et al.*[18] indicate that when an unrestricted regression is conducted and parameters are not subjectively fixed *a priori* more reliable data-driven final estimates are obtained. Using a completely unrestricted model building process, the patients' age centered on its median of 5 months turned out to be a better covariate than body weight.

We found dosing requirements necessary to achieve and maintain a desired serum concentration change rapidly during the first year of life. Specifically, between 2 months and 12 months of age, the bolus dose required decreases with age. This likely reflects developmental changes. To account for this finding, we highlight a range for the bolus dose in the dosing recommendations shown in table 6. Children close to 2 months old require a larger bolus (*e.g.*, 12 mg/kg to maintain 20 μg/ml) and those close to 12 months old require a lower loading dose (*e.g.*, 6 mg/kg to maintain 20 μg/ml). In the very young group, there is little variation in the dose required between newborn and 2 months old. For the oldest group (>12 months), the recommendations are nearly identical to those reported in older children by Grassin-Delyle *et al.*[17] and in adults by Dowd *et al.*[8]

All the patients in our study underwent continuous ultrafiltration and the mean concentration of TXA in the ultrafiltrate collected at the end of CPB was approximately 243 μg/ml. There was no difference in systemic clearance (CL), central volume of distribution (V_1), intercompartmental clearance (Q), or peripheral volume of distribution (V_2) with and without CPB in the group of patients who had both continuous ultrafiltration plus MUF when compared with the group that only received continuous ultrafiltration. This suggests that the use of MUF does not have a significant impact on the dosing requirements. All patients underwent ultrafiltration with hemoconcentration. The volume of ultrafiltrate, when tested as a covariate for the structural pharmacokinetic parameters, did not reach statistical significance to enter the model. However, because the TXA concentrations in the ultrafiltrate at the end of CPB were comparable with those in the plasma, the process arguably extends the distribution and elimination of the drug. Nonetheless, it does not contribute to interindividual variability in TXA levels. Similarly, the use of hypothermia and circulatory arrest did not impact the interindividual variability of TXA levels.

Our results clearly reveal that the use of CPB affects the pharmacokinetics of TXA, as reported in adults by Dowd *et al.*[8] and Bojko *et al.*[19] More recently, Grassin-Delyle *et al.*[17] reported that CPB influences the distribution and clearance in children.[17] However, our analysis did not support their use of the single term $(V_{CPB}/500)^{\theta CPB}$ for all pharmacokinetic parameters in the model. Our modeling of CPB as a time event and the estimation of the whole set of parameters separately prior and during CPB greatly improved the goodness of fit and the reliability of the final parameters. Superimposed on the age effect, the CPB prime volume exerts a major influence on the pharmacokinetics of TXA as shown in tables 5 and 6. It significantly increases the steady-state volume of distribution as would be expected from the nature of the process. However, the range of values reported in the literature (table 5) may be related to how both age and CPB effects have been modeled.

We chose to base the CPB prime dose on prime volume rather than on body weight. This is important because in infants and children the body weight to pump prime volume ratio varies widely across age groups. This also provides a method to accommodate for variation in the prime volumes that might be used in different institutions. It should be noted that the ideal CPB prime dose would be based not on the total CPB prime volume but on the plasma volume of the CPB prime: ([100 – Hct]/100) • (CPB prime volume); however, this seems to be unnecessarily cumbersome.

The need to better define the "correct" TXA concentration range takes on added importance, given the association between high plasma TXA concentrations and seizures or seizure-like activity in adult cardiac surgical patients.[20–23] Whether there is a similar problem in infants and children receiving TXA is unclear at present. However, the fact that seizure activity in the postoperative period after infant cardiac surgery is highly associated with worsened long-term neurodevelopmental outcome is important in this context.[24] All our patients were seen at 24 and 48 h, and no seizures were reported during their hospitalizations. In addition, we have exposed 500 to 600 children/yr over the last 15 yr to the plasma levels of TXA reported here without evidence of TXA-related seizure activity. In our practice, the maximal plasma levels of TXA are reached during general anesthesia conducted with relatively high doses of midazolam and fentanyl along with low-dose inhalation agent and neuromuscular blockade. It is conceivable that in an awake or lightly sedated patient seizure activity in association with these, high TXA levels would be observed.

This study provides a comprehensive population pharmacokinetic analysis of TXA in neonates and young children undergoing complex cardiac surgery. Currently, concentrations of TXA that are effective and safe remain uncertain. The dosing schedules provided here allow clinicians to target specific plasma concentrations in children of different ages. As demonstrated in figure 7, A–C, a dosing schedule using a sequence of three bolus injections and no continuous infusion, as proposed by Chauhan *et al.*,[4] is unlikely to be effective unless very large bolus doses with resultant high peak plasma levels are administered. Otherwise, given the elimination half-life of the drug, subtherapeutic concentrations are bound to occur. Our analysis also makes it apparent that a single dose schedule used across all age ranges to achieve a desired plasma TXA concentration is unlikely to be effective. A limitation of our study is that a model validation in an independent cohort of patients has not yet been performed.

Acknowledgments

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

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Wesley: Division of Cardiac Anesthesia, Boston Children's Hospital, 300 Longwood Avenue, Boston, Massachusetts 02115. mark.wesley@childrens.harvard.edu. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. Anesthesiology's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

References

1. Reid RW, Zimmerman AA, Laussen PC, Mayer JE, Gorlin JB, Burrows FA: The efficacy of tranexamic acid *versus* placebo in decreasing blood loss in pediatric patients undergoing repeat cardiac surgery. Anesth Analg 1997; 84:990–6
2. Chauhan S, Das SN, Bisoi A, Kale S, Kiran U: Comparison of epsilon aminocaproic acid and tranexamic acid in pediatric cardiac surgery. J Cardiothorac Vasc Anesth 2004; 18:141–3
3. Pasquali SK, Li JS, He X, Jacobs ML, O'Brien SM, Hall M, Jaquiss RD, Welke KF, Peterson ED, Shah SS, Jacobs JP: Comparative analysis of antifibrinolytic medications in pediatric heart surgery. J Thorac Cardiovasc Surg 2012; 143:550–7
4. Chauhan S, Bisoi A, Kumar N, Mittal D, Kale S, Kiran U, Venugopal P: Dose comparison of tranexamic acid in pediatric cardiac surgery. Asian Cardiovasc Thorac Ann 2004; 12:121–4
5. Couturier R, Rubatti M, Credico C, Louvain-Quintard V, Anerkian V, Doubine S, Vasse M, Grassin-Delyle S: Continuous or discontinuous tranexamic acid effectively inhibits fibrinolysis in children undergoing cardiac surgery with cardiopulmonary bypass. Blood Coagul Fibrinolysis 2014; 25:259–65
6. Eaton MP: Antifibrinolytic therapy in surgery for congenital heart disease. Anesth Analg 2008; 106:1087–100
7. Horrow JC, Van Riper DF, Strong MD, Grunewald KE, Parmet JL: The dose-response relationship of tranexamic acid. Anesthesiology 1995; 82:383–92
8. Dowd NP, Karski JM, Cheng DC, Carroll JA, Lin Y, James RL, Butterworth J: Pharmacokinetics of tranexamic acid during cardiopulmonary bypass. Anesthesiology 2002; 97:390–9
9. Grassin-Delyle S, Tremey B, Abe E, Fischler M, Alvarez JC, Devillier P, Urien S: Population pharmacokinetics of tranexamic acid in adults undergoing cardiac surgery with cardiopulmonary bypass. Br J Anaesth 2013; 111:916–24
10. Sigaut S, Tremey B, Ouattara A, Couturier R, Taberlet C, Grassin-Delyle S, Dreyfus JF, Schlumberger S, Fischler M: Comparison of two doses of tranexamic acid in adults undergoing cardiac surgery with cardiopulmonary bypass. Anesthesiology 2014; 120:590–600
11. Yee BE, Wissler RN, Zanghi CN, Feng C, Eaton MP: The effective concentration of tranexamic acid for inhibition of fibrinolysis in neonatal plasma *in vitro*. Anesth Analg 2013; 117:767–72
12. Soslau G, Horrow J, Brodsky I: Effect of tranexamic acid on platelet ADP during extracorporeal circulation. Am J Hematol 1991; 38:113–9
13. Stief T: Effect of tranexamic acid on mortality in patients with traumatic bleeding: Prespecified analysis of data from randomised controlled trial. Tranexamic acid might stop severe bleeding by intrinsic generation of thrombin. BMJ 2012; 345: e5839
14. Goobie SM, Meier PM, Pereira LM, McGowan FX, Prescilla RP, Scharp LA, Rogers GF, Proctor MR, Meara JG, Soriano SG, Zurakowski D, Sethna NF: Efficacy of tranexamic acid in pediatric craniosynostosis surgery: A double-blind, placebo-controlled trial. Anesthesiology 2011; 114:862–71
15. Eriksson O, Kjellman H, Pilbrant A, Schannong M: Pharmacokinetics of tranexamic acid after intravenous administration to normal volunteers. Eur J Clin Pharmacol 1974; 7:375–80
16. Ririe DG, James RL, O'Brien JJ, Lin YA, Bennett J, Barclay D, Hines MH, Butterworth JF: The pharmacokinetics of epsilon-aminocaproic acid in children undergoing surgical repair of congenital heart defects. Anesth Analg 2002; 94:44–9
17. 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
18. Björkman S, Oh M, Spotts G, Schroth P, Fritsch S, Ewenstein BM, Casey K, Fischer K, Blanchette VS, Collins PW: Population pharmacokinetics of recombinant factor VIII: The relationships of pharmacokinetics to age and body weight. Blood 2012; 119:612–8
19. Bojko B, Vuckovic D, Mirnaghi F, Cudjoe E, Wasowicz M, Jerath A, Pawliszyn J: Therapeutic monitoring of tranexamic acid concentration: High-throughput analysis with solid-phase microextraction. Ther Drug Monit 2012; 34:31–7
20. Murkin JM, Falter F, Granton J, Young B, Burt C, Chu M: High-dose tranexamic Acid is associated with nonischemic clinical seizures in cardiac surgical patients. Anesth Analg 2010; 110:350–3
21. Schwinn DA, Mackensen GB, Brown EN: Understanding the TXA seizure connection. J Clin Invest 2012; 122:4339–41
22. Koster A, Börgermann J, Zittermann A, Lueth JU, Gillis-Januszewski T, Schirmer U: Moderate dosage of tranexamic acid during cardiac surgery with cardiopulmonary bypass and convulsive seizures: Incidence and clinical outcome. Br J Anaesth 2013; 110:34–40
23. Kalavrouziotis D, Voisine P, Mohammadi S, Dionne S, Dagenais F: High-dose tranexamic acid is an independent predictor of early seizure after cardiopulmonary bypass. Ann Thorac Surg 2012; 93:148–54
24. Bellinger DC, Wypij D, Rivkin MJ, DeMaso DR, Robertson RL Jr, Dunbar-Masterson C, Rappaport LA, Wernovsky G, Jonas RA, Newburger JW: Adolescents with d-transposition of the great arteries corrected with the arterial switch procedure: Neuropsychological assessment and structural brain imaging. Circulation 2011; 124:1361–9