PHARMACOKINETICS

Pharmacokinetics of tranexamic acid in neonates and infants undergoing cardiac surgery

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AIM

Tranexamic acid (TXA) continues to be one of the antifibrinolytics of choice during paediatric cardiac surgery. However, in infants less than 1 year of age, the optimal dosing based on pharmacokinetic (PK) considerations is still under discussion.

METHODS

Forty-three children less than 1 year of age were enrolled, of whom 37 required the use of cardiopulmonary bypass (CPB) and six were operated on without CPB. Administration of 50 mg kg^{-1} TXA intravenously at the induction of anaesthesia was followed by 50 mg kg^{-1} into the CPB prime in the CPB group. Plasma concentrations of TXA were analysed by gas chromatography–mass spectrometry. PK data were investigated using nonlinear mixed-effect models.

RESULTS

A two-compartment model was fitted, with the main covariates being allometrically scaled bodyweight, CPB, postmenstrual age (PMA). Intercompartmental clearance (Q), peripheral volume (V2), systemic clearance, (CL) and the central volume (V1) were calculated. Typical values of the PK parameter estimates were as follows: CL = 3.78 [95 % confidence interval (CI) 2.52, 5.05] l h^{-1}; central volume of distribution = 13.6 (CI 11.7, 15.5) l; Q = 16.3 (CI 13.5, 19.2) l h^{-1}; V2 = 18.0 (CI 16.1, 19.9) l. Independently of age, 10 mg kg^{-1} TXA as a bolus, a subsequent infusion of 10 mg kg^{-1} h^{-1}, then a 4 mg kg^{-1} bolus into the prime and a reduced infusion of 4 mg kg^{-1} h^{-1} after the start of CPB are required to maintain TXA concentrations continuously above 20 μg ml^{-1}, the threshold value for an effective inhibition of fibrinolysis and far lower than the usual peak concentrations (the '10-10-4-4 rule').

CONCLUSIONS

The introduction of a modified dosing regimen using a starting bolus followed by an infusion and a CPB prime bolus would prohibit the potential risk of seizures caused by high peak concentrations and also maintain therapeutic plasma concentration above 20 μg ml^{-1}.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Tranexamic acid remains the cornerstone of antifibrinolytic therapy during paediatric cardiac surgery.
- Side effects are rare, but could include seizures and thrombosis.
- Better dosing regimens are warranted to avoid unnecessary high concentrations and subsequent complications.

WHAT THIS STUDY ADDS

- Paediatric doses are different to those for adults.
- The main covariates are allometrically scaled bodyweight, on or off cardiopulmonary bypass (CPB), and postmenstrual age.
- Concentrations within the therapeutic range can be achieved by using a dosing schedule including a starting bolus followed by an infusion and a CPB prime bolus.

Table of Links

LIGANDS
Tranexamic acid

This Table lists key ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1].

Introduction

Tranexamic acid (TXA) has been used to reduce blood loss in cardiac surgery following its first proof of effectiveness in 1990 [2]. As aprotinin has been withdrawn from the market in many countries, only two lysine analogues remain as the main antifibrinolytics – namely, TXA and ε-aminocaproic acid. TXA is considered to be the most effective [3] but significant side effects have been reported, including dose-dependent seizures after cardiac surgery [4]. Therefore, in order to optimize its use, new studies have examined the pharmacokinetic (PK) profile in different patient populations [5, 6]. As a quality improvement exercise, we examined TXA PK with our standard dosing regimen. We expected the TXA PK in neonates and infants to be mostly influenced by dilutional effects during cardiopulmonary bypass (CPB), age, weight and renal function. The goal of our study was to quantify these covariates with a population approach in these age groups and to determine the effects of CPB. Based on these findings, we suggest a dosing recommendation for patients less than 1 year of age. As our study differs, in terms of patient population and bypass management, from the two studies published so far in this age group [7, 8], it provides valuable new information on this topic.

Methods

Clinical protocol

The study was approved by the ethics committee of the Medical Faculty of the Technical University Munich (ref.

5600/12) and registered with the World Health Organization International Clinical Trials Registry Platform/German Clinical Trials Register No. DRKS-4538. Written parental consent was obtained in all cases. Patients were children less than 1 year of age with a congenital heart defect undergoing cardiac surgery with ($n = 37$) or without ($n = 6$) CPB between January and June 2013. Exclusion criteria were a known allergy to TXA; any coagulopathy, as defined by laboratory levels outside the norm, adjusted for age; or preoperative renal insufficiency. Per standard protocol, 50 mg kg^{-1} TXA was given over 5 s after induction and arterial line placement. If CPB was used, another 50 mg kg^{-1} was added to the prime volume. Anaesthesia was induced and maintained with midazolam, sufentanil and pancuronium. Volume replacement before CPB was accomplished with albumin 5% or Ringer's acetate. The CPB priming fluid included Ringer's acetate, 5000 IU of heparin, 100–150 ml washed packed red blood cells, 100–150 ml fresh frozen plasma and sodium bicarbonate. The final prime volumes achieved were approximately 370–380 ml. A noncoated bypass circuit was used. Depending on the patient's size, either a Dideco D100 for neonates <5 kg (Sorin Group, Milan, Italy) or a Terumo Baby RX oxygenator (Terumo, Ann Arbor, MI, USA) was used. Mild hypothermia at 32–34°C was applied on CPB. After discontinuation of CPB and routine modified ultrafiltration (MUF), protamine was administered in a heparin : protamine ratio of 1:1.3. Additional protamine was based on residual heparin levels. Our institutional transfusion management was applied and haemoglobin levels were maintained above 10 g dl^{-1}.

Sample acquisition, handling, and processing

Blood samples (1.2 ml) were drawn into ethylene diamine tetra-acetic acid-coated tubes (Sarstedt, Nuembrecht, Germany). After induction of anaesthesia, a radial or femoral artery catheter was inserted, TXA was injected and samples were drawn after 5, 15, 30, 60, 90, 120, 150, 180, 240 and 360 min or until CPB was initiated as dictated by clinical circumstances. Additional samples were drawn before the initiation of CPB and 5, 15, 30, 60, 90, 120, 150, 180, 240 and 360 min after the start of CPB. Plasma was separated by centrifugation (4000 g, 10 min) at room temperature and stored at −80°C.

Tranexamic acid assay

Plasma concentrations were analysed by gas chromatography–mass spectrometry using a published analytical amino-acid quantification method [9] adapted to TXA (see Appendix). A relative mean intra-assay recovery of 92.6±3.7 % (n = 49) was measured at a concentration level of 122 μg ml^{-1}, with an interassay coefficient of variation of 12.9 %. The calibration curve was linear (r^2 = 0.99995) and the lower limit of quantification (LLOQ) was 4.6 μg ml^{-1}.

Data analysis

Descriptive analysis was performed using PASW Statistics v21.0 (IBM Corporation, Somer, NY, USA).

PK modelling

Structural model. PK data were analysed using the nonlinear mixed-effects modelling software Phoenix 64 NLME 7.0 (Certara Inc., Princeton, NJ, USA) [10]. The fixed parameters are elimination (CL) and intercompartmental (Q) clearances, and the volume of the central (V1) and peripheral (V2) compartments. A two-compartment open model without covariates was first fitted to our TXA data.

Covariate analysis. Using a forward addition procedure, the following covariate effects were tested, based on physiological and developmental principles during the first year of life: weight, postmenstrual age (PMA), CPB prime volumes, CPB as a categorical variable (on/off) and modified ultrafiltration (MUF) volumes. All covariates were centred to the adult values and their effects was estimated as θ_{cov}. We evaluated three approaches for body size, one with no normalization, one in which parameters were normalized for weight, and an allometric approach in which the PK parameters were allometrically scaled for bodyweight (BW). Individual values of PK parameters (P_i) were described for BW as follows:

$$P_i = \text{tvP} * (\text{BW}_i/70 \text{ kg})^{\theta\text{weight}}$$

where i denotes the ith individual and tvP the typical value for the population. The power exponents θ were tested with and without fixation at 0.75 for the clearance and 1 for the volume parameters (allometric scaling) [11].

θ_{CPB} was introduced as a modifying factor and estimated using NLME during the period of CPB:

$$P_i = \text{tvP}^* \exp[\theta_{CPB}^*(CPB = 1)] \text{ CR for the effect of CPB as}$$
a categorical variable

where P_i denotes a clearance or volume term for the ith individual, tvP is the typical parameter value, CPB is a binary variable (θ_{CPB} 1 = θ_{CPB} when on CPB, θ_{CPB} 0 = 0 otherwise), with θ_{CPB} as the influential parameter. For the impact of age on clearance, a sigmoidal maturation function (Fmat) based on the postmenstrual age was chosen:

$$Fmat = \frac{1}{1 + \left(\frac{PMA50}{PMA}\right)^{\theta\text{PMA}}}$$

with PMA being postmenstrual age in years, θPMA the Hill coefficient and PMA50 the maturation half-life [11].

Model evaluation and selection. The likelihood ratio test (-2LL), Akaike information criterion (AIC) and Bayesian information criterion (BIC) were used to test different hypotheses regarding the final model. The final residual variability (ε_{PROP}) was described using a proportional error model. From the final model, 1000 simulations were performed to generate a visual predictive check (VPC) [12]. The goodness-of-fit plots were examined, with particular emphasis on the observed *vs.* the population-predicted concentrations for the best predictive model. The results were visualized as a scatterplot for the population conditional weighted residuals (CWRES) *vs.* individual predicted concentrations or time after dose and a prediction-corrected VCP (pcVPC) stratified for BW (n = 1000 simulations). A nonparametric bootstrap analysis *(n = 1000 samples)* was used to assess parameter precision.

Simulation of TXA concentrations. For the simulation, patient BWs of 2.5, 5, 7.5 and 10 kg were chosen. Using the final model, concentration courses were simulated for the first 8 h, assuming a 60-min interval between the first dose and initiation of CPB with an additional duration of CPB of 90 min. We considered 20 μg ml^{-1} a reasonable lower border of the therapeutic window during the time of surgery as previously proposed [13, 14]. This target concentration was selected to minimize any possible proconvulsive effects while maintaining clinical efficacy.

Results

Population characteristics and TXA concentrations

The demographic and CPB characteristics are listed in Table 1.

One terminal sample was missing because the child required cardiopulmonary resuscitation shortly before the final sampling point. A total of 637 samples were obtained, with three outliers excluded and no sample below the LLOQ. Notable side effects related to TXA were a series of three seizures on the day of the operation in one infant [15]. Individual PK courses of TXA are shown in Figure 1. Measured peak concentrations were 213 ± 54 μg ml^{-1} (mean ± standard deviation) 5 min after the first bolus, and the TXA concentration fell to 75 ± 19 μg ml^{-1} shortly before CPB.

Table 1

Demographics and cardiopulmonary bypass (CPB) characteristics

Demographics	*n* = 43
Age, days (min–max)	123 (6–348)
Weight, kg (min–max)	4.95 (2.3–9.5)
Length, cm	58 ± 9
Male gender (%)	22 (51)
Cyanosis (%)	15 (35)
Aristotle basic score, median (25–75% percentile)	8 (6–9)
CLCREA, mean ± standard deviation (ml min^{-1} 1.73m^{-2}) (min–max)	75 ± 29 (26–149)
CPB characteristics	*n* = 37
Priming volume (ml)	382 ± 65
Packed red blood cell volume in the prime (ml)	113 ± 17
Fresh frozen plasma volume in the prime (ml)	100 ± 0
CPB time (min)	82 ± 34
Cross-clamping *n* (%)	27 (73)
Cross-clamp time (min)	49 ± 29

CLCREA, estimated preoperative creatinine clearance using the Schwartz formula

The second dose, on CPB, achieved a peak level of 236 ± 67 µg ml^{-1}. 5.6 ± 0.43 h after the start of CPB, measured concentrations were 54 ± 15 µg ml^{-1}. The six patients without CPB had residual TXA concentrations of 26 ± 10 µg ml^{-1} 6 h after their first dose.

Population PK modelling

The model building steps are summarized in Table 2. Significant covariates of the final model were allometrically scaled BW, CPB as a categorical covariate and PMA, but not MUF or prime volume. First, we evaluated three approaches to normalizing the PK parameters to BW. Compared with a covariate-free model, the weight-standardized model improved the objective function. The allometric model yielded a further improvement and was retained. Thereafter, adding the effect of PMA on CL and CPB again improved the model. The addition of prime or MUF volumes did not improve the model beyond the categorical effects of CPB (not shown).

The final covariates used in the model with the lowest BIC values therefore were: allometrically fixed BW using theory-based exponents of 0.75 on (CL, Q) and 1 on (V1, V2); CPB on (Q, V2, CL) and PMA on CL.

Table 3 shows the final population PK estimates, with the typical values for BW groups presented in Table 4. Figures 2 and 3 compare the covariate-free to the final model. In Figure 2, the initial asymmetrical distribution observed for the covariate-free model is corrected to a slightly more homogenous distribution when the covariates are taken into account. Figure 3 depicts the pcVPC for the final model.

Simulation of TXA concentrations

As allometric BW, CPB and PMA were the main covariates, we proposed a weight-adjusted scheme (Table 4). Despite the benefits conferred by the introduction of allometric scaling into our final model, we retained a weight-adjusted dosing regimen based on the allometric PK parameters for adult BW values as dosing based on BW satisfies most clinical situations in the operating room [16]. Therefore, concentration curves for children of less than 10 kg BW were simulated after receiving a loading dose of 10 mg kg^{-1} TXA, followed by a continuous infusion of 10 mg kg^{-1} h^{-1} until initiation of CPB, then a 4 mg kg^{-1} bolus, followed by a 4 mg kg^{-1} h^{-1} infusion to maintain a target blood concentration of 20 mg l^{-1}. This is known as the '10-10-4-4' rule (Figure 4).

Discussion

We have described TXA PK in infants less than 1 year of age undergoing cardiac surgery with and without CPB but omitting those with deep hypothermic circulatory arrest. Using a two-compartmental model, model improvements from baseline were seen by adding allometric scaling of BW, CPB as a categorical factor and PMA. Finally, a dose recommendation was developed to ensure a threshold concentration of 20 mg l^{-1}, which can be described as the '10-10-4-4 rule'.

The effect of covariates on PK

The two main aspects of PK disturbances on bypass are distribution and elimination. For TXA, Dowd *et al.* [13] found that, in adults, CPB induced an increase in V_c (V1). Haemodilution has been described to be responsible for an increase in the apparent V_c [17]. The impact of haemodilution is mostly apparent upon initiation of CPB and is more pronounced in neonates [18], where prime volumes often exceed 100% of the patient's blood volume. Therefore redosing on CPB seems justified to compensate for this drop in concentration. Previous studies in adults reported either concentrations only [19] or a full set of PK parameters [7, 13, 20]. Recently, paediatric data in children undergoing cardiac surgery [7, 8] and craniofacial surgery [21] have been presented.

Our study was an extension of the previous work by Grassin-Delyle *et al.* [7] that investigated children with a mean age of 5 years and only showed an effect of CPB on Q. By contrast, Wesley *et al.* [8], in children less than 4 years of age, found an effect of CPB on volume and clearance parameters. Our results did not reveal an effect of CPB on V1. However, using a model including V1 was only marginally worse and actually provided the best AIC and -2LL values. Therefore, we were able to confirm the findings by Wesley *et al.* that favour an unrestricted model centred on the median of the respective population parameter. During our model-building process, the clearance maturation was clearly dependent on PMA. This is explained primarily by the renal excretion of TXA and the fast maturation of the glomerular filtration rate: at birth, it is approximately 35% of adult values, reaching 50% at 48 weeks PMA and 90 % at
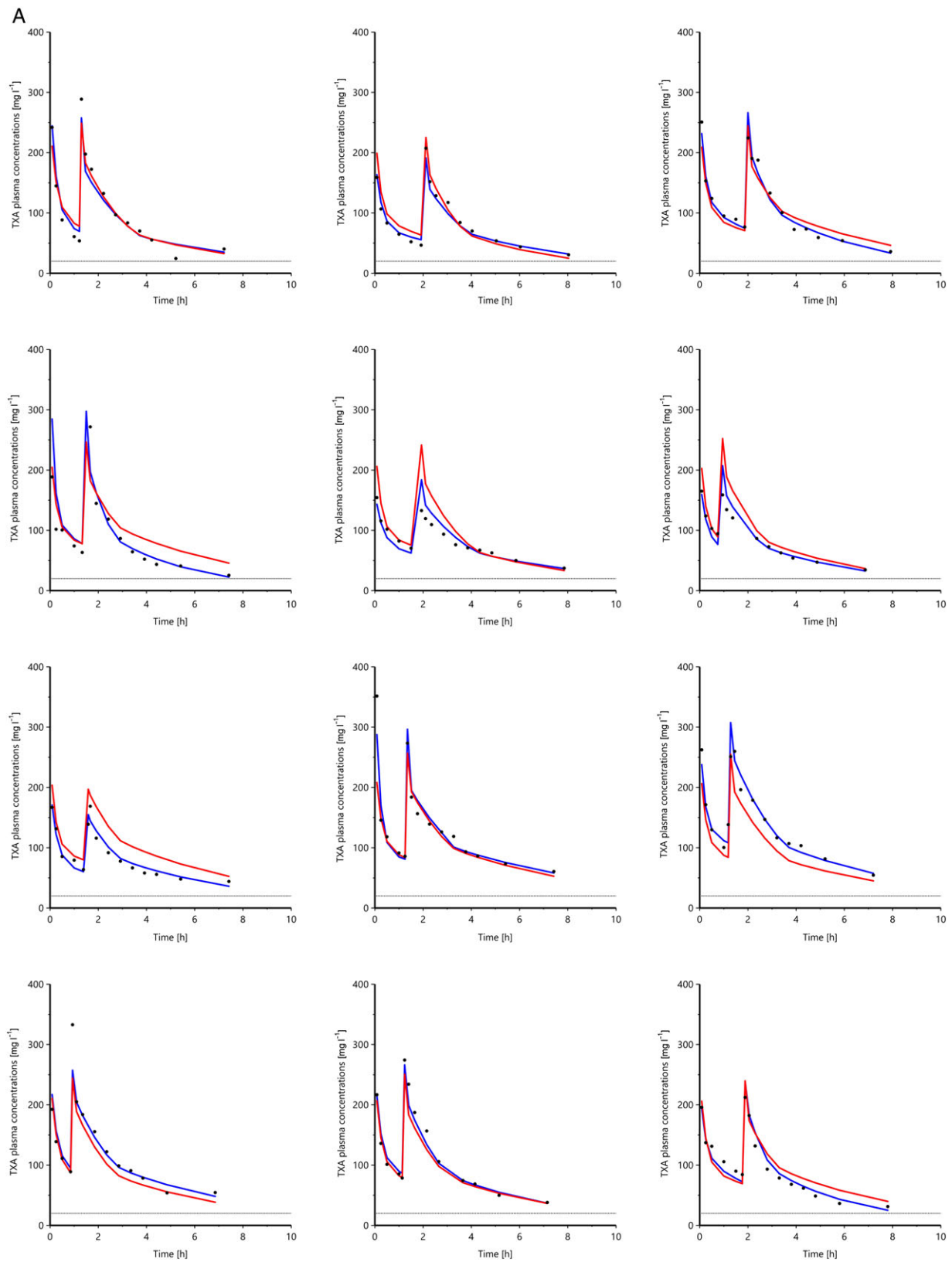
Figure 1

Latticed scatter plot by indi vidual, containing all population observations, population predictions (red lines) and individual predictions (blue lines) *vs.* time. The first dose was applied at the time zero and the second dose was given upon initiation of cardiopulmonary bypass (if used), 5 min before the second peak. TXA, tranexamic acid
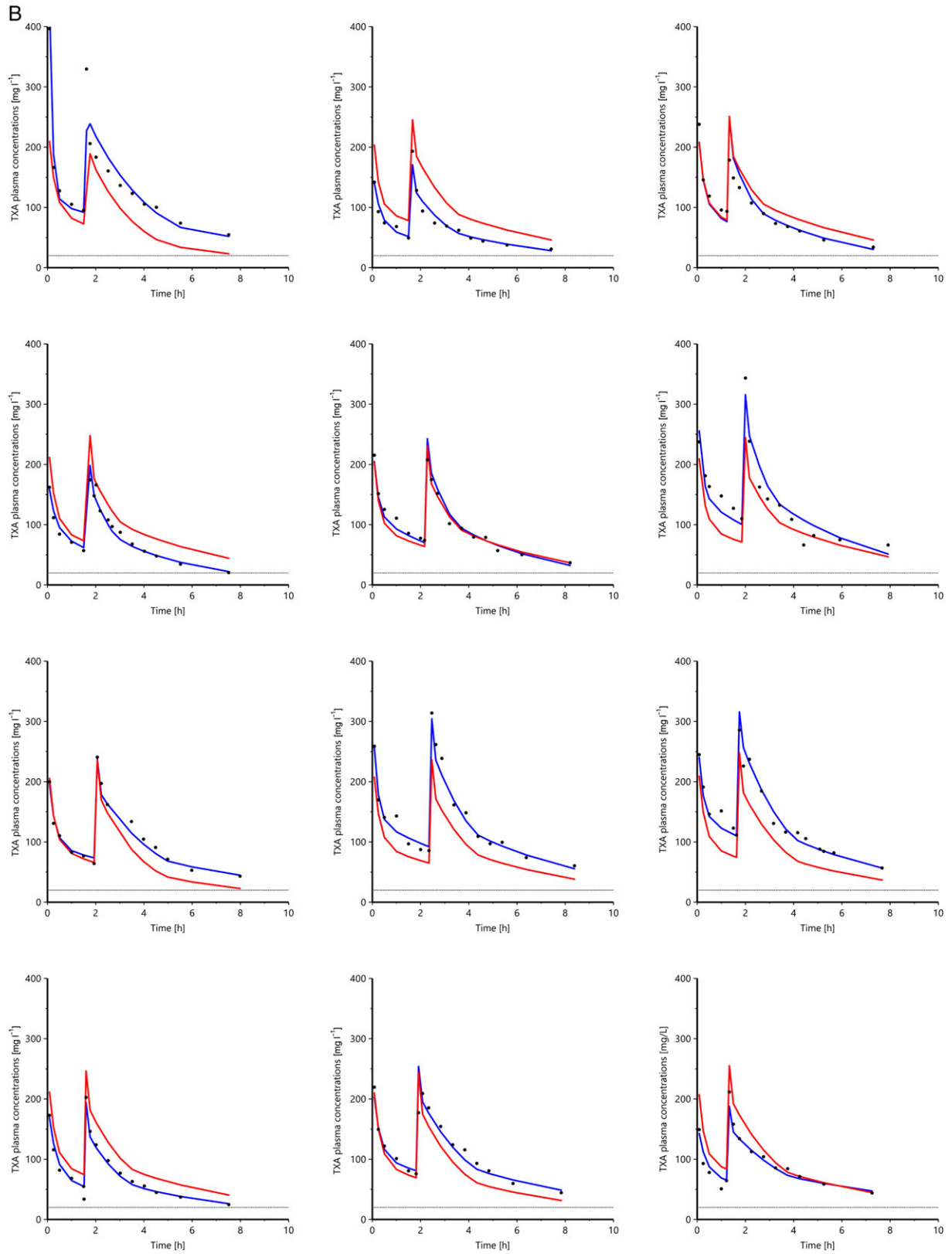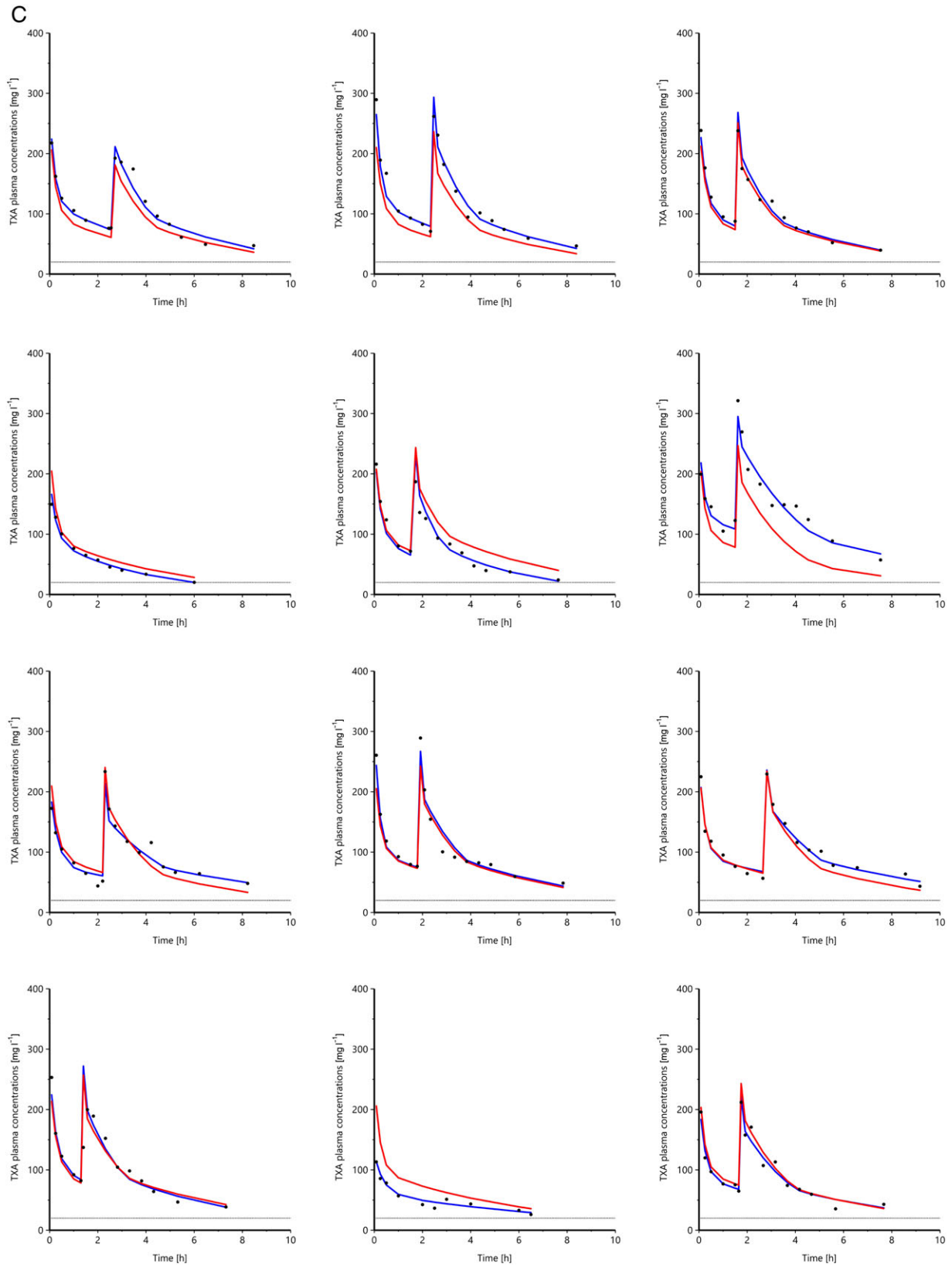
Figure 1

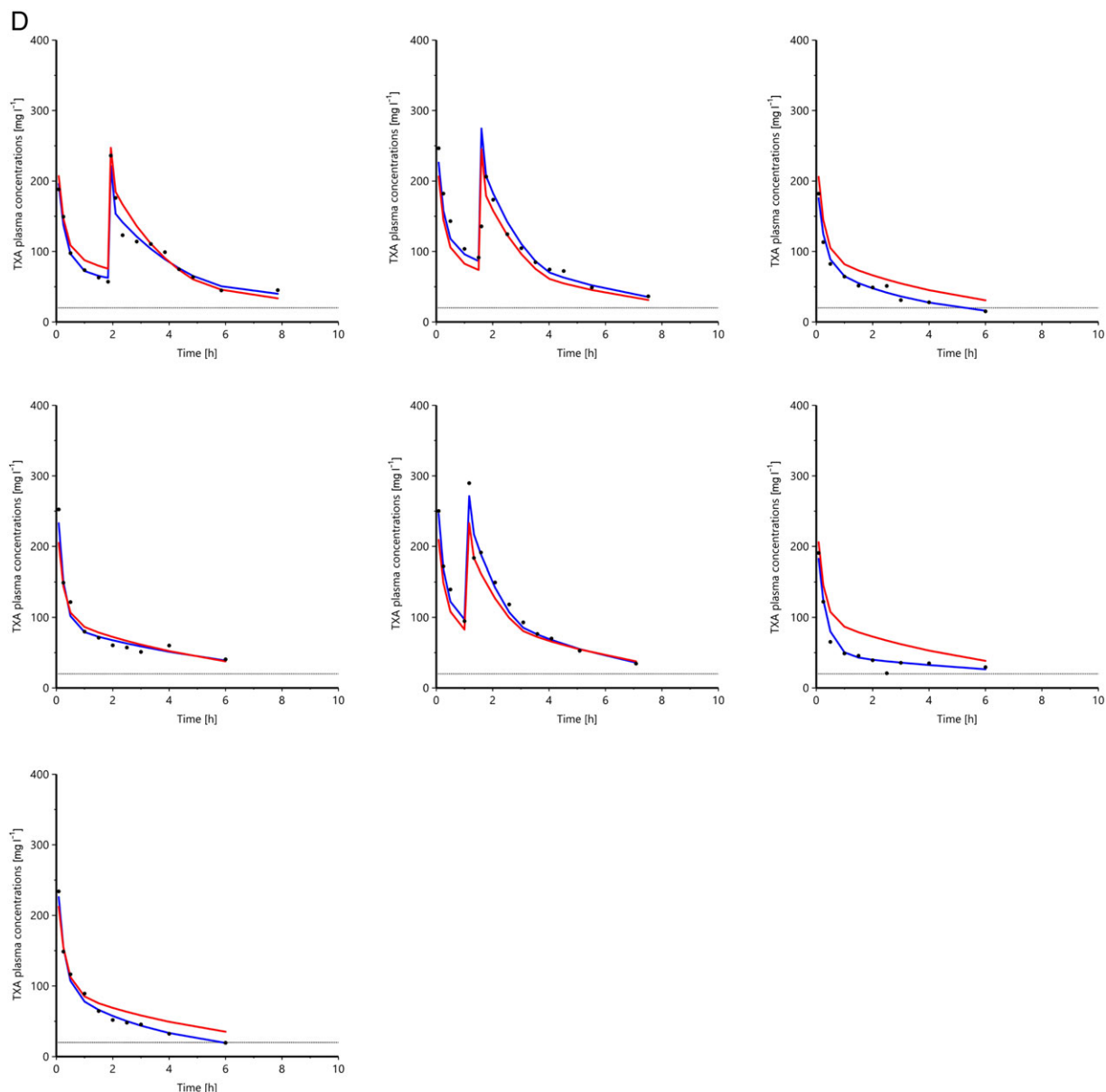(Continued)

Figure 1
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1 year postnatal age [22]. All children had a normal preoperative creatinine clearance according to the Schwartz formula and values were found to be within the range for 'noncardiac' children [21]. Taken together, our estimates are in the range of previously published ones in paediatric patients [7, 8, 21], as well as adult values (Table S1) [13, 19, 20, 23, 24].

Dosing and range of effective concentrations

The primary aim of the present study was to reduce peak levels and the total amount of TXA administered. We propose a dosing regimen based on our PK model (Table 4). This involves slightly higher doses than those proposed by Wesley *et al.* [8], (with a loading dose of 9–15 mg kg^{-1}, an infusion rate of 2.0–2.5 mg kg^{-1} h^{-1} and a

CPB prime dose of 20 mg l^{-1}) and that reported by Grassin-Delyle *et al.* [7] (with a loading dose of 6.4 mg kg^{-1} followed by an infusion rate of 2.0–3.1 mg kg^{-1} h^{-1} without a prime bolus) based on data from older children with a mean BW of 18 kg. The main reasons for the higher doses indicated in the present study and a different approach to PK analysis. We created a simulation with only 90 min of CPB time, whereas Wesley *et al.* presented their analysis using an ongoing effect of CPB from its initiation onwards. In comparison, the combination of these two probably increases the clearance (CL) and our model may be more realistic during regular bypass with mild hypothermia. An additional bolus into the CPB prime avoids exaggerated dilutional effects on CPB [25]. Also, the TXA boulus into the prime fluid was higher since our prime volumes were also slightly higher. In contrast

Table 2

Model building summary, base scenario with allometric weight on (V1, V2, CL, Q), sorted by BIC

Additional covariates	−2LL	AIC	BIC	Number of parameters
None	5616	5636	5680	10
CPB (V2, V1)	5609	5633	5686	12
CPB (V2)	5613	5635	5684	11
CBP (V1)	5611	5633	5682	11
CPB (V2, V1), PMA (CL)	5595	5621	5679	13
CPB (V2), PMA (CL)	5600	5624	5677	12
CPB (V1), PMA (CL)	5597	5621	5675	12
PMA (CL)	5602	5624	5673	11
CPB (Q, V2)	5593	5617	5671	12
CPC (Q)	5595	5617	5666	11
CPB (Q, V2, V1)	5582	5608	5666	13
CPB (Q, V2), PMA (CL)	5579	5605	5663	13
CPB (Q, V1)	5584	5608	5662	12
CPB (Q), PMA (CL)	5580	5604	5658	12
CPB (Q, V2, V1), PMA (CL)	5568	5596	5658	14
CPB (Q, V1), PMA (CL)	5570	5596	5653	13
CPB (CL)	5489	5511	5560	11
CPB (Cl), PMA (CL)	5478	5502	5556	12
CPB (V1, CL)	5467	5491	5544	12
CPB (V1, CL), PMA (CL)	5456	5482	5540	13
CPB (V2, CL)	5448	5472	5526	12
CPB (V2, CL), PMA (CL)	5439	5465	5522	13
CPB (V2, V1, CL)	5391	5417	5475	13
CPB (V1, V1, CL), PMA (CL)	5383	5411	5473	14
CBP (Q, V1, CL)	5378	5404	5462	13
CPB (Q, V1, CL), PMA (CL)	5368	5396	5459	14
CPB (Q, CL)	5379	5403	5456	12
CPB (Q, CL), PMA (CL)	5369	5395	5453	13
CPB (Q, V2, V1, CL)	5348	5376	5438	14
CPB (Q, V2, V1, CL), PMA (CL)	**5339**	**5369**	5436	15
CPB (Q, V2, CL)	5350	5376	5434	13
CPB (Q, V2, CL), PMA (CL)	5341	5369	**5432**	14

−2LL, minus two times the log likelihood; weight allometric= bodyweight with theta values fixed to 0.75 (CL, Q) and 1 (V1, V2)
AIC, Akaike information criterion; BIC, Bayesian information criterion; CL, systemic clearance; CPB, cardiopulmonary bypass; PMA, postmenstrual age; Q, intercompartmental clearance; V1, central volume of distribution; V2, peripheral volume of distribution. Bold number, the lowest values for the model quality parameters

to Wesley *et al.* [8], we did not find a different TXA dose requirement in the neonatal group.

Any dosing recommendation in our investigation is aiming at target plasma TXA concentration of 20 mg l^{-1}. This target is a topic of great discrepancy; the main target concentrations in the literature range from 10 µg ml^{-1} to 126 µg ml^{-1} [13, 19]. *In vivo*, higher doses may be clinically

more effective in reducing the perioperative blood loss [13], even though this did not translate into differences in mortality [26]. We used one of the lowest effective target concentrations reported, based on the work by Yee *et al.* [14]. These authors explored the maximal inhibitory effects of TXA on fibrinolysis *in vitro*. Using pooled cord blood from term neonates, they induced fibrinolysis with 1000 IU ml^{-1}

Table 3

Final population parameters

| Individual parameters | All 43 patients | | | |
	Typical value (tv) estimate (%RSE)	IIV (%RSE)	Bootstrap median (%RSE)	IIV (%RSE)
$V1 (l) = tvV1 * (weight/70)^{\theta weight} * exp^{(\eta V1)}$	13.58 (7.0)	0.101 (45.8)	13.77 (7.3)	0.105 (66)
θ weight	1 (0)		1 (0)	
$V2 (l) = tvV2 * (weight/70)^{\theta weight} * exp^{(\theta CPB *(CPB==1))} * exp^{(\eta V2)}$	17.99 (5.4)	0.090 (32.9)	17.92 (5.5)	0.092 (34.3)
θ CPB	-0.153 (30.8)		−0.157 (31.8)	
θ weight	1 (0)		1 (0)	
$CL (l\ h^{-1}) = tvCL * (weight/70)^{\theta weight} *1/(1 + (PMA50/PMA)^{\theta PMA}) * exp^{(\theta CPB *(CPB==1))} *exp^{(\eta Cl)}$	3.78 (12.6)	0.067 (18.3)	3.66 (25.3)	0.063 (19.3)
θ CPB	0.842 (7.7)		0.843 (8.0)	
θ weight	0.75 (0)		0.75 (0)	
θ PMA	2.95 (46.0)		3.02 (619)	
PMA50	0.632 (14.5)		0.679 (42.0)	
$Q (l\ h^{-1}) = tvQ * (weight/70)^{\theta weight} * exp^{(\theta CPB *(CPB = 1))} * exp^{(\eta Q)}$	16.32 (8.7)	9.92 E-06 (6.3)	16.14 (8.8)	1.53E-05 (541)
θ CPB	1.87 (13.0)		1.88 (14.9)	
θ weight	0.75 (0)		0.75 (0)	
Standard deviation of the multiplicative error mode	0.128		0.127	

CL, elimination clearance; CPB, cardiopulmonary bypass; IIV, interindividual variability; %RSE, percent relative standard error, PMA50, PMA at which normalized clearance is equal to 50% of the maximum value (in years); Q, intercompartmental clearance; V1, central volume of distribution; V2, peripheral volume of distribution

Table 4

Dosing proposal and mean pharmacokinetic parameters for tranexamic acid in children undergoing cardiac surgery with cardiopulmonary bypass (CPB) for a 20 µg ml^{-1} minimum target concentration

Weight (kg)	CPB	CL (l h^{-1})	V1 (l)	Q (l h^{-1})	V2 (l)	Fast t½ (h)	Slow t½ (h)	First dose (mg kg^{-1})	Rate (mg kg^{-1} h^{-1})	CPB dose (mg kg^{-1})	Rate post-CPB (mg kg^{-1} h^{-1})
10	0	0.932	2.101	3.79	2.75	0.191	4.11	10	10	4	4
	1	2.16	2.101	24.7	2.36	0.028	1.54				
7.5	0	0.728	1.511	3.05	2.01	0.171	3.83	10	10	4	4
	1	1.691	1.511	19.9	1.72	0.025	1.43				
5	0	0.506	0.997	2.25	1.35	0.155	3.64	10	10	4	4
	1	1.177	0.997	14.7	1.16	0.023	1.36				
2.5	0	0.213	0.517	1.34	0.70	0.139	4.51	10	10	4	4
	1	0.494	0.517	8.74	0.60	0.020	1.72				

CL, elimination clearance; fast t½, primary elimination half-life; Q, intercompartmental clearance; slow t½, terminal elimination half-life; V1, central volume of distribution; V2, peripheral volume of distribution

tissue plasminogen activator (t-PA), and titrated TXA to complete inhibition. Effective inhibitory concentrations to abolish fibrinolysis were found at TXA plasma concentrations of 6.54 µg ml^{-1}, 17.5 µg ml^{-1} and 9.83 µg ml^{-1} for neonatal plasma, adult plasma and a mixture of both, respectively, during routine paediatric CPB. One limitation of their study was the fact that normal plasma levels of t-PA in children on CPB are only between 2.5 IU ml^{-1} and 4 IU ml^{-1} [27, 28], so the applied t-PA concentration was more than 250 times higher. Despite this, the study underlined the concept of maintaining TXA concentrations around 20 µg ml^{-1}. This is particularly important in light of the increasing risk of seizures to 2.5 –3.5% in adult cardiac surgery patients at doses greater than 100 mg kg^{-1} of TXA [29]. In fact, one of our
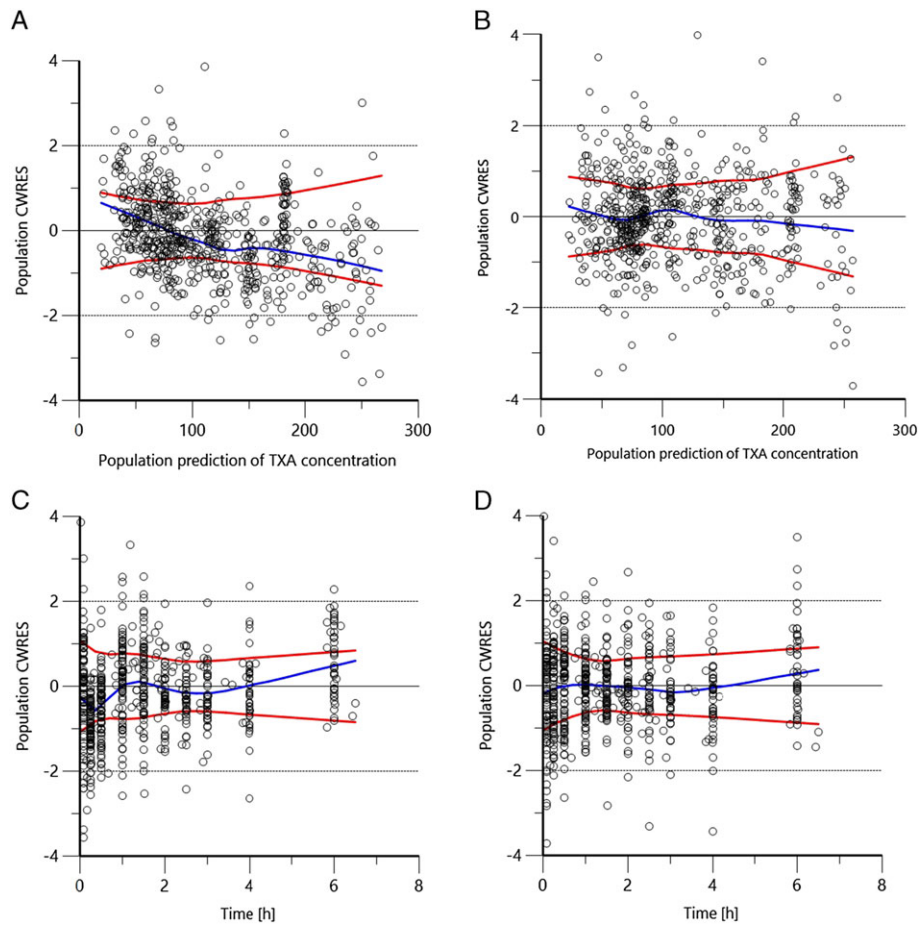
Figure 2

Development of the predictive performance of the population CWRES against concentration or time after dose. (A), (C): covariate free model. (B), (D): final model. Values should be between $y=-2$ and $y=+2$. Blue line= Normal Loess smooth line, Red lines= Absolute Loess regression lines. CWRES, conditional weighted residuals
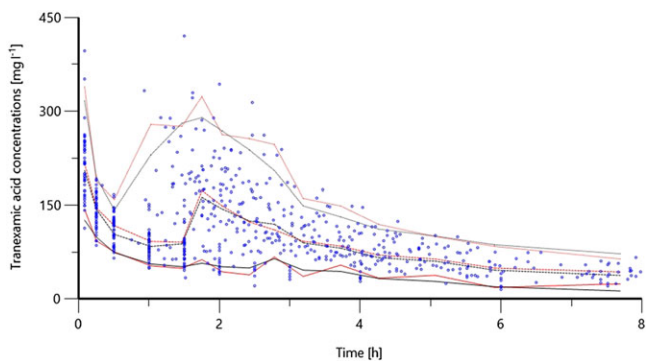

Figure 3

Visual predictive check from a Monte Carlo simulation ($n = 1000$) of the final model. Raw data points as well as predicted (black) and observed (red) 5th, 50th and 95th percentiles are shown
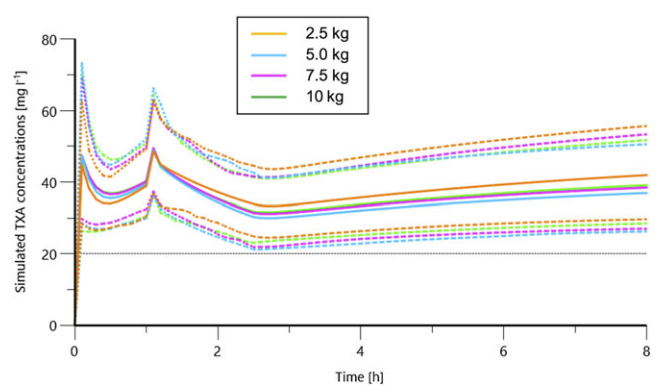
Figure 4

Simulation of concentration curves using the final model with the '10-10-4-4' dosing recommendations for tranexamic acid (TXA) [a loading dose of 10 mg kg^{-1} followed by a continuous infusion of 10 mg kg^{-1} h^{-1} until initiation of cardiopulmonary bypass (CPB), then a 4 mg kg^{-1} bolus, followed by 4 mg kg^{-1} h^{-1} after CPB] for maintaining a target concentration of 20 mg l^{-1}. Means and 2.5th and 97.5th percentiles are given

patients suffered a series of seizures 6 h after the second dose of TXA [15], possibly related to the recently discovered competitive antagonism of TXA at glycine and GABA$_A$

receptors [30, 31] and the fact that peak cerebrospinal fluid (CSF) levels are delayed by approximately 5–6 h [30]. In addition, changes in the blood–brain barrier after CPB [32] might be responsible for unexpectedly high CSF levels, which are even higher in neonates and infants with a naturally more fragile endothelium.

Limitations

All of the children in our study underwent continuous ultrafiltration and MUF. As we did not take separate samples before and after MUF, or standardize the filtration process, we cannot comment on its effect on TXA plasma concentrations. However, introducing MUF volumes as a covariate did not improve the model. In addition, the effect of moderate and deep hypothermia on TXA levels is unclear and we limited our population to cases using mild hypothermia between 32°C and 36°C [33]. This is in agreement with the study by Wesley *et al.* [8] where neither MUF nor hypothermia were found to be influential factors.

Conclusions

We investigated TXA PK in children of less than 1 year of age undergoing cardiac surgery. PK parameters are significantly influenced by BW, maturation and CPB. A simple dosing regimen of 50 mg kg^{-1} twice at the beginning and repeated on CPB delivers effective TXA concentrations above 20 μg ml^{-1} until 6 h after the last dose but at the risk of high peak concentrations, which eventually lead to seizures. Alternatively, a reduced dosing regimen according to desired target concentrations of e.g. 20 μg ml^{-1} throughout surgery would comprise the '10-10-4-4 rule': an initial bolus of 10 mg kg^{-1} is followed by an infusion of 10 mg kg^{-1} h^{-1} until initiation of CPB and then a 4 mg kg^{-1} h^{-1} infusion after the start of CPB, with a bolus of 4 mg kg^{-1} into the CPB prime. Further studies should aim to relate these results to pharmacodynamics – in this case, the associated blood loss and clinical outcome – as demonstrated in adults by Sigaut *et al.* [26].

Competing Interests

There are no competing interests to declare.

Contributors

R.G. helped to design the study, conduct the study, recruit the patients, collect the data, analyse the data and write the manuscript. M.G. helped to design the study, analyse the data and write the manuscript. S.G.-D. helped to analyse the data and write the manuscript. S.U. helped to analyse the data and write the manuscript. K.M. helped to design the study, conduct the study, recruit the patients, collect the data, analyse the data and write the manuscript. P.T.-P. helped to design the study, analyse the data and write the manuscript. S.B. helped to conduct the study, collect the data, analyse the data and write the manuscript. S.B. helped to analyse the data and write the manuscript. G.W. helped to design the study, conduct the study, analyse the data and write the manuscript. All authors approved the final manuscript.

Appendix

An Agilent GCMS (5890 plus and 5972 MSD) system in electron impact (EI) mode was used. Plasma preparation started by adding 1 μg (10 μl) internal standard solution ^{13}C,^{15}N-tranexamic acid (Sigma, Steinheim, Germany) and 1 μg 6-aminohexanoic acid (AHA;10 μl, Sigma) to a 25 μl sample. Deproteination was achieved with an additional volume of 150 μl of cold methanol (–20°C) (Baker, Deventer, the Netherlands). The mixture was centrifuged at 3200 *g* for 4 min, the pellet was washed twice with 25 μl methanol/H$_2$O [4/1 (vol/vol)] and the combined supernatants were dried in an N$_2$ stream at 40°C. The residual was resolved in 50 μl water, 25 μl methanol and 6 μl pyridine (Acros, Fisher scientific, Nidderau, Germany). Methylchloroformate (Sigma) was added in two portions of 5 μl each with intercepted mixing. The derivatives were shifted into an organic phase by adding 50 μl of CHCl$_3$ (Sigma). The lower CHCl$_3$ phase was transferred into micro-inserts (CZT, Kriftel, Germany). The chromatographical setup was: injection volume 0.3 μl (splitless for 0.5 min at 285°C), a Phenomenex ZB-1 ms capillary column with dimensions of 30 m × 0.25 mm × 0.25 μm (Phenomenex, Aschaffenburg, Germany). Mass spurs (m/z) and retention times (RT) of the substances: internal standards isotopic enhanced TXA (m/z = 201.1; RT = 6.654 min) and AHA (m/z = 172.1; RT = 5.737 min) and target TXA (m/z = 198.1; RT = 6.654 min). The used temperature characteristic as follows: starting with 70°C for 1 min, a subsequent gradient of 30 K min^{-1} up to 280°C was used. Calibration was found to be linear over the whole concentration range.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

http://onlinelibrary.wiley.com/doi/10.1111/bcp.13274/suppinfo

Table S1 Kinetic parameters for comparative pharmacokinetic studies separated into paediatric and adult data, as available