British Journal of Anaesthesia **114** (4): 689–99 (2015)
Advance Access publication 13 January 2015 · doi:10.1093/bja/aeu459

BJA

Population pharmacokinetics of ε-aminocaproic acid in adolescents undergoing posterior spinal fusion surgery

P. A. Stricker[1]*, M. R. Gastonguay[2], D. Singh[1], J. E. Fiadjoe[1], E. M. Sussman[1], E. Y. Pruitt[1], T. K. Goebel[1] and A. F. Zuppa[3]

[1] Department of Anesthesiology and Critical Care Medicine, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA
[2] Metrum Institute, Tariffville, CT, USA
[3] Department of Anesthesiology and Critical Care Medicine, Division of Critical Care Medicine, Department of Pediatrics, Division of Clinical Pharmacology and Therapeutics, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

* Corresponding author. E-mail strickerp@email.chop.edu

Editor's key points

- There are no pharmacokinetic data available to guide dosing of ε-aminocaproic acid (EACA) in children.
- The pharmacokinetic properties of EACA were modelled in adolescents undergoing spinal fusion for scoliosis.
- The data were used to recommend weight-based EACA dosing, which should be validated in prospective efficacy trials.

Background. Despite demonstrated efficacy of ε-aminocaproic acid (EACA) in reducing blood loss in adolescents undergoing spinal fusion, there are no population-specific pharmacokinetic data to guide dosing. The aim of this study was to determine the pharmacokinetics of EACA in adolescents undergoing spinal fusion surgery and make dosing recommendations.

Methods. Twenty children ages 12–17 years were enrolled, with 10 children in each of two groups based on diagnosis (idiopathic scoliosis or non-idiopathic scoliosis). Previously reported data from infants undergoing craniofacial surgery were included in the model to enable dosing recommendations over a wide range of weights, ages, and diagnoses. A population non-linear mixed effects modelling approach was used to characterize EACA pharmacokinetics.

Results. Population pharmacokinetic parameters were estimated using a two-compartment disposition model with allometrically scaled weight and an age effect on clearance. Pharmacokinetic parameters for the typical patient were a plasma clearance of 153 ml min^{-1} 70 kg^{-1} (6.32 ml min^{-1} $kg^{-0.75}$), intercompartmental clearance of 200 ml min^{-1} 70 kg^{-1} (8.26 ml min^{-1} $kg^{-0.75}$), central volume of distribution of 8.78 litre 70 kg^{-1} (0.13 litre kg^{-1}), and peripheral volume of distribution of 15.8 litre 70 kg^{-1} (0.23 litre kg^{-1}). Scoliosis aetiology did not have a clinically significant effect on drug pharmacokinetics.

Conclusions. The following dosing schemes are recommended according to patient weight: weight <25 kg, 100 mg kg^{-1} loading dose and 40 mg kg^{-1} h^{-1} infusion; weight ≤ 25 kg–<50 kg, 100 mg kg^{-1} loading dose and 35 mg kg^{-1} h^{-1} infusion; and weight ≥ 50 kg, 100 mg kg^{-1} loading dose and 30 mg kg^{-1} h^{-1} infusion. An efficacy trial employing this dosing strategy is warranted.

Clinical trial registration. NCT01408823.

Keywords: antifibrinolytic agents; paediatrics; pharmacology; scoliosis; spinal fusion

Accepted for publication: 15 October 2014

Posterior spinal fusion (PSF) surgery can be associated with significant blood loss, and perioperative transfusion is very common. Various strategies have been devised to decrease intraoperative blood loss and reduce transfusions in adolescents and children undergoing PSF. The intraoperative administration of the antifibrinolytic drug ε-aminocaproic acid (EACA) is one strategy with demonstrated efficacy.

Although there have been positive efficacy trials evaluating EACA for reduction of blood loss and transfusion requirements in children undergoing PSF, close review of the literature reveals that while dosing regimens are consistent, the rationale for dose selection is unclear.[1–8] EACA pharmacology has been well studied in adults;[9–14] however, there are no paediatric pharmacokinetic (PK) data to guide dose selection for adolescents undergoing PSF. Based on our PK data in infant craniofacial surgery, we hypothesized that the dosing strategy of a 100 mg kg^{-1} loading dose followed by 10 mg kg^{-1} h^{-1} infusion used in prior spinal fusion surgery efficacy studies fails to achieve concentrations deemed therapeutic. The primary objective of this study was to describe the PKs of EACA administered to

children and adolescents undergoing PSF. The secondary objective was to combine PK data from older children and adolescents in this study with PK data from a cohort of infants in a previous study to provide dosing guidance to achieve target concentrations across a range of ages, diagnoses, and weights.

Methods

Clinical trial

This analysis includes data from both a prospective PK trial in children ages 8–18 years undergoing PSF for idiopathic and non-idiopathic scoliosis and previously reported data from an open-label, non-randomised, dose escalation PK trial in infants ages 2–24 months undergoing craniofacial surgery.[15]

The adolescent scoliosis study was a single-centre, prospective PK study conducted in subjects undergoing PSF (http://www.clinicaltrials.gov; NCT01408823). The study was conducted following institutional review board approval and written informed consent and subject assent. Males and females ages 8–18 years undergoing PSF surgery for scoliosis for whom EACA administration was planned as part of standard care by the anaesthesiology team were eligible for enrolment. Subjects who did not have a parent or legal guardian who spoke English and subjects with a history of abnormal renal function were excluded. An evaluable subject was defined as any enrolled subject who had at least seven PK blood samples drawn and was not withdrawn from the study for other reasons. After eligibility was verified and informed consent and assent (when appropriate) were obtained, subjects were assigned to one of two groups based on their diagnosed scoliosis aetiology: an idiopathic scoliosis group and a non-idiopathic scoliosis group. Subjects were enrolled until there were 10 evaluable subjects in each of the two study groups (total of 20 subjects).

Details regarding trial conduct for the craniofacial study were previously reported.[15] Briefly, this was a dose-escalating trial involving 18 subjects divided into three cohorts of six infants. The first cohort received a 25 mg kg^{-1} loading dose followed by a continuous intravenous infusion (CIVI) of 10 mg kg^{-1} h^{-1}; the second cohort received a 50 mg kg^{-1} loading dose followed by a CIVI of 20 mg kg^{-1} h^{-1}; the third cohort received a 100 mg kg^{-1} loading dose followed by a CIVI of 40 mg kg^{-1} h^{-1}.

Administration of EACA

In the PSF trial, EACA dosing was determined by our local institutional practice, which is based on the regimen reported in adolescents undergoing spinal fusion: a 100 mg kg^{-1} loading dose followed by a CIVI of 10 mg kg^{-1} h^{-1}.[2–4 7 8] EACA administration began in the operating room following induction of anaesthesia after vascular access was obtained. The EACA loading dose was administered over 10 min using a programmed infusion pump and was followed by the CIVI until skin closure. In one subject the anaesthesiologist limited the maximum loading dose to 5 g of EACA (for a total of 80 mg kg^{-1} as a loading dose). Patient information and data pertaining to the medical management and perioperative course of enrolled subjects were collected, including age, weight, gender, diagnosis, surgical procedure, duration of surgery, and estimated blood loss.

Conduct of anaesthesia

All subjects received general tracheal anaesthesia with standard American Society of Anesthesiologists monitoring. Mask induction of anaesthesia was performed with sevoflurane, nitrous oxide, and oxygen. To facilitate intraoperative monitoring of somatosensory evoked potentials and transcranial electric motor evoked potentials, anaesthesia was maintained with intravenous (i.v.) infusions of propofol, an opioid (remifentanil or fentanyl), and in some subjects, ketamine. Additional parenteral opioids (fentanyl, hydromorphone, morphine, methadone) were administered for anaesthetic supplementation and postoperative analgesia. Each subject had two peripheral i.v. catheters and a radial arterial catheter placed as part of standard management. In six cases a central venous catheter was inserted at the discretion of the anaesthesiologist; all of these were in the non-idiopathic group. Maintenance of normothermia was facilitated using forced air convection blanket warmers and an i.v. fluid warmer. Anaesthetic management, fluid management, and blood loss replacement were at the discretion of anaesthesia providers without a fixed protocol.

PK sampling

For the subjects undergoing PSF surgery, PK samples (1 ml of blood) were drawn immediately before and after the loading dose, after initiation of CIVI (0.5, 2, 3, and 4 h), at the end of CIVI, and following the end of CIVI (0.5, 2, 4, and 6 h), for a maximum of 11 PK samples per subject. Intraoperative PK samples were drawn from the arterial catheter. During the postoperative period, blood was drawn from the arterial catheter when present, or from a blood-drawing i.v. catheter. If neither was present, samples were drawn together with routine postoperative laboratory blood draws and the time of phlebotomy was recorded. Blood samples were collected in Microtainer tubes (BD, Franklin Lakes, NJ, USA) containing lithium heparin and stored at 4°C for up to 12 h prior to centrifugation and separation of plasma. Samples were centrifuged at 3500 rpm at 4°C for 15 min. Plasma was separated and stored at −80°C. Details regarding PK sampling in the craniofacial population are described in our previous publication.[15]

Drug quantitation

A selective and highly sensitive method for the determination of EACA in human plasma was developed and fully validated based on high-performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS). Sample preparation involved dilution with 10% acetic acid and addition of the internal standard aminoheptanoic acid. To 50 μl of each plasma sample, 1.0 ml of 10% acetic acid in water was added. After vortexing, a 50 μl aliquot of the diluted sample was transferred and mixed with 50 μl of internal standard working solution (2 μg ml^{-1}) and 5 ml of water, and 300 μl of each sample was transferred to a 96-well plate and centrifuged

at 3500 rpm for 10 min. Then 5 μl of the sample was injected into the HPLC-MS/MS machine for analysis. EACA was separated by HPLC and detected with MS/MS in positive ionization mode with multiple reaction monitoring. A gradient program was used to elute the analytes using 0.1% formic acid in water as mobile phase A and methanol as mobile phase B, at a flow rate of 0.5 ml min^{-1}. Calibration curves showed linearity (coefficient of regression, $r^2 > 0.99$) over the concentration range of 1.0–500 mcg ml^{-1}. Intraday precision based on the standard deviation of replicates of the lower limit of quantification (LLOQ) was 6.50%, and for quality control, samples ranged from 3.31 to 12.8%. Accuracy ranged from 111% and 96.0–106% for LLOQ and quality control samples. The interday precision was 17.0% and 4.89–11.46% for LLOQ and quality control samples, and the accuracy was 94.9 and 91.6–104% for LLOQ and quality control samples. Stability studies showed that EACA was stable both during sample preparation and storage. The method was validated for EACA concentrations of 1–250 mcg ml^{-1}; the lower limit of quantitation was 1 mcg ml^{-1}. If the EACA concentration was higher than the upper limit of validated quantitation, samples were diluted (1:4 or 1:10) and reanalysed.

Pharmacostatistical analysis

Model building

The population PK analysis was conducted using non-linear mixed effects methods (NONMEM software, ICON Development Solutions, Ellicott City, MD, USA, version VI, level 2.0 with subroutines ADVAN 3, TRANS 4). All models were run with the first-order conditional estimation with interaction (FOCE-I) method. S-Plus version 6.2 (Insightful, Data Analysis Products Division, Seattle, WA, USA) was used for goodness-of-fit diagnostics and graphical displays. The goodness-of-fit from each model run was assessed by examination of the following criteria: diagnostic plots; standard errors of the parameters; global minimization of the search algorithm; the Akaike Information Criterion, which is equal to the minimum objective function value (MOFV) plus two times the number of parameters; and plausibility of parameter estimates.

Base model

One- and two-compartment models were investigated. A two-compartment disposition model was selected to define the EACA plasma concentration profile based on results from the model-building process and previously published data.[9 11] Models were parameterized by clearance (Cl, ml min^{-1}), intercompartmental clearance (Q, ml min^{-1}), central volume of distribution (V1, litres), and peripheral volume of distribution (V2, litres). The one-compartment model was inadequate to describe the data.

An exponential variance model was used to describe the variability of PK parameters across individuals in the form $P_i = \theta_k \exp(\eta_{ki})$, where P_i is the estimated parameter value for the individual subject i, θ_k is the typical population value of parameter k, and η_{ki} is the interindividual random effects for individual i and parameter k. Interindividual variability was initially estimated for clearance and then subsequently for the remaining PK parameters.

Additive, proportional, and combined (additive and proportional) residual error models were considered during the model-building process. Ultimately a combined additive and proportional error model was used to describe random residual variability: $C_{obs,ij} = (C_{pred,ij} * (1 + \varepsilon_{ijP})) + \varepsilon_{ijA}$, where $C_{obs,ij}$ is the observed concentration j in individual i, $C_{pred,ij}$ is the individual predicted concentration, ε_{ijP} is the proportional residual random error, and ε_{ijA} is the additive residual random error for individual i and measurement j.

The impact of weight on all parameters was implemented using an allometric model: $TVP = \theta_{TVP} * (WT_i / WT_{ref})^{\theta allometric}$, where TVP is the typical value of a model parameter, described as a function of body weight, θ_{TVP} is an estimated parameter describing the typical PK parameter value for an individual with weight equal to the reference weight, WT_i is body weight, WT_{ref} is the reference value (70 kg for this analysis), and $\theta^{allometric}$ is an allometric power parameter based on physiologic consideration of size on metabolic processes, fixed at 0.75 for clearances and at 1 for volumes.[16 17]

Full covariate model

A full covariate model was constructed in order to make inferences about effects of covariates on EACA disposition. Covariate effects were predefined based on clinical interest, prior knowledge, and physiologic plausibility. The analysis was focused on estimation of effects and avoided the problem of selection bias, which is particularly problematic with stepwise model building in small data sets.[18 19] The effects of age and diagnosis were evaluated in this model. Blood loss was not evaluated in the model because it was not measured in a time-dependent fashion, did not account for administration of blood products, and was correlated with diagnosis.

Dosing guidance

Once estimates of Cl were obtained via the model-building process, the steady-state concentrations (C_{ss}) that would be achieved with a linearly scaled weight-based dosing strategy were simulated across a range of weights, assuming full Cl maturation, using the equation

$$C_{ss}\,(\text{mg litre}^{-1}) = \frac{\text{Infusion rate (mg h}^{-1})}{\text{Cl (litre h}^{-1})}.$$

The estimated random intersubject variability for Cl was used to calculate a 95% population prediction interval for Cl for a specific weight (WT), using the equations

$$\text{lower bound of Cl (highest } C_{ss}) = \text{TVCl} * \left(\frac{\text{WT}}{70}\right)^{0.75} * \exp(-1.96 * \text{SD})$$

$$\text{higher bound of Cl (lowest } C_{ss}) = \text{TVCl}^{*}\left(\frac{\text{WT}}{70}\right)^{0.75} {}^{*}\exp(+1.96 * \text{SD}),$$

where TVCl is the typical value of Cl for the population at reference covariate values and SD is the estimated standard deviation of the interindividual random effects for Cl. Based on previous literature that a plasma concentration of at least 130 mg litre^{-1} of EACA was required to control systemic fibrinolytic activity,[20 21] linear weight-based dosing strategies to achieve a C_{ss} of 130 mg litre^{-1} at the lower 2.5th quantile of the C_{ss} were calculated based on the allometrically derived Cl estimate for individual weights and ages. Weights were assigned to specific ages using the US Centers for Disease Control growth charts for girls 0–36 months of age. Based on our final model, full maturation of the age effect was completed by 15 months of age, and age was therefore not included in the Cl estimates past 15 months.

Similarly, the full covariate model was used to simulate expected concentrations for a population of subjects in each of the three diagnoses. Simulated concentration time profiles were performed for a population of children with idiopathic scoliosis (typical weight 55 kg, age 187.5 months), non-idiopathic scoliosis (typical weight 33.7 kg, age 165 months), and craniofacial surgery (typical weight 8.8 kg, age 37 weeks). Profiles were simulated after each population received a 100 mg kg^{-1} bolus over 10 min followed by CIVI of 10 mg kg^{-1} h^{-1} for 4 h, which was the dosing regimen used in the scoliosis population. As concentrations >130 mg litre^{-1} have been targeted for therapeutic EACA effects,[20 21] additional dosing schemes were evaluated in each population to determine the dose that would achieve a C_{ss} >130 mg ml^{-1} in >97.5% of subjects, using estimates of interindividual variability.

Results

Study conduct

For the PSF population, 45 patients were screened for enrolment. Of these, 23 were eligible for the study and 21 were approached for enrolment. Of these, 20 subjects were enrolled in the study, all of whom were evaluable and subsequently included in the PK analysis. Diagnoses of evaluable PSF subjects are presented in Table 1. Diagnoses for infants undergoing craniofacial surgery are described in our previous publication[15] but are presented in Table 2 for comparison. A summary of PK study variables for all study groups is presented in Table 3.

The craniofacial population was younger, weighed less, had a higher percentage of PK samples drawn in the postoperative period as opposed to the intraoperative period, and had the shortest duration of surgery. Our previous analysis of the craniofacial population indicated that intraoperative EACA Cl was less than the postoperative Cl. This analysis was possible in the craniofacial population because PK sampling occurred almost equally intraoperatively and postoperatively. Since the majority of PK samples in the PSF population occurred in the intraoperative setting (where Cl is reduced based on the previous analysis), we anticipated that a combined model would result in an underestimate of population Cl. Therefore diagnosis was evaluated as a covariate in the combined model that included the craniofacial and PSF populations. In addition, we did not compare intraoperative and postoperative clearances in the PSF population since there were so few postoperative samples.

Table 1 Posterior spinal fusion subject characteristics

	ID	Weight, kg	Age, years	Diagnosis	Spinal levels operated on	Estimated blood loss, ml	Estimated blood loss, ml kg^{-1}
Idiopathic group	1	66.7	15	Idiopathic kyphoscoliosis	T4–L3	900	13.5
	3	38.1	14	Idiopathic scoliosis	C7–T11	600	15.7
	5	49.3	15	Idiopathic scoliosis	T2–L1	700	14.2
	6	55.9	14	Idiopathic kyphoscoliosis	T4–L4	200	3.6
	8	62.6	17	Idiopathic kyphoscoliosis	T1–L2	650	10.4
	9	57.9	13	Idiopathic scoliosis	T4–L4	850	14.7
	10	62.2	15	Idiopathic kyphoscoliosis	T3–L1	900	14.5
	11	55.1	16	Idiopathic kyphoscoliosis	T3–L3	750	13.6
	13	44.5	16	Idiopathic scoliosis	T4–L2	700	15.7
	15	49.1	14	Idiopathic scoliosis	T2–L1	750	15.3
Non-idiopathic group	2	40.7	14	Neurofibromatosis type 1	T2–L3	2000	49.1
	4	45.4	16	Ehlers–Danlos syndrome	T2–L2	525	11.6
	7	33.7	12	Cerebral palsy	T2–L5	800	23.7
	12	32.1	14	Congenital neuromuscular scoliosis	T4–L2	250	7.8
	14	58.2	12	Syringomyelia with early onset scoliosis	T2–L3	500	8.6
	16	49.2	13	Cortical dysgenesis, absence of corpus callosum, neuromuscular scoliosis	T4–L4	550	11.2
	17	29.8	13	Cerebral palsy, chronic static encephalopathy	T2–L5	1800	60.4
	18	31.6	16	Spina bifida	T2–L5	1300	41.1
	19	33.7	12	Marfan's syndrome	T2–L2	1000	29.7
	20	32.0	13	22q deletion with early onset scoliosis	T2–L3	900	28.1

Table 2 Characteristics of subjects undergoing craniofacial reconstruction surgery from prior study[15]

	ID	Weight, kg	Age, weeks	Diagnosis	Procedure
Cohort 1	1	7.7	27.4	Unicoronal synostosis	Fronto-orbital advancement
	2	9.6	38.9	Metopic synostosis	Fronto-orbital advancement
	3	7.9	31.6	Lambdoid synostosis	Posterior cranial vault reconstruction
	4	11.4	85.9	Pfeiffer syndrome	Fronto-orbital advancement
	5	8.3	38.6	Unicoronal synostosis	Fronto-orbital advancement
	6	7.8	34.6	Saethre–Chotzen syndrome	Fronto-orbital advancement
Cohort 2	7	10.8	67.1	Sagittal synostosis	Fronto-orbital advancement
	8	6.7	69.4	Metopic synostosis	Fronto-orbital advancement
	9	8.9	99	Metopic synostosis	Fronto-orbital advancement
	10	6.8	33	Unicoronal synostosis	Fronto-orbital advancement
	11	9.9	34.9	Metopic synostosis	Fronto-orbital advancement
	12	7.4	30.6	Metopic synostosis	Fronto-orbital advancement
Cohort 3	13	8.7	35	Metopic synostosis	Fronto-orbital advancement
	14	11.8	106.9	Sagittal synostosis	Posterior cranial vault reconstruction
	15	9.1	42.1	Metopic synostosis	Fronto-orbital advancement
	16	10.9	48.7	Metopic synostosis	Fronto-orbital advancement
	17	7.1	36.4	Metopic synostosis	Fronto-orbital advancement
	18	10.2	43.7	Unicoronal synostosis	Fronto-orbital advancement

Table 3 Summary of pharmacokinetic (PK) study variables

	Idiopathic scoliosis, median (range)	Non-idiopathic scoliosis, median (range)	Craniofacial reconstruction, median (range)
Age	187.5 months (158–211)	165 months (148–199)	39 weeks (27–107)
Weight, kg	55.5 (38.1–66.7)	33.7 (29.8–58.2)	8.8 (6.7–11.8)
% PK samples postoperatively	18 (12–33)	28 (12–40)	68 (40–80)
Surgery duration, min	389 (325–580)	468 (288–645)	220 (112–343)
CIVI duration, min	340 (270–498)	395 (244–596)	243 (111–365)

PK modelling and simulation

Semi-log plots of EACA concentration–time profiles for the three study groups are presented in Figure 1. Most doses resulted in steady-state concentrations during the operative procedure lower than the target of 130 mg ml^{-1}. This was not seen in the highest dosing cohort of craniofacial children, who received a larger dose (100 mg kg^{-1} loading dose followed by CIVI of 40 mg kg^{-1} h^{-1}).

The final structural model was a two-compartment disposition model with interindividual random effects estimated on Cl, V1 and V2. Using FOCE-I estimation, the base model minimized with successful execution of the covariance matrix of the estimates. Scaling the PK parameters allometrically to weight resulted in a 153-point improvement in the minimum value of the objective function (MVOF) compared with a model without weight. The addition of an interindividual variability estimate on Q resulted in less precise parameter estimates (the SE on the Cl estimate increased from 6.99 to 34.24) and poor model stability, and therefore was not included in the final model.

The full covariate model was developed by simultaneously including effects for covariates of clinical interest and those with physiologic plausibility. Despite no improvement with the MOFV, age and diagnosis were included in the final model to estimate the magnitude and precision of these effects on Cl. As part of model building, the impact of the correlation of age and surgery type on the parameter effect estimates of age were evaluated, and this parameter was unchanged with or without the inclusion of surgery type. Given the full covariate model, the impact of potential correlation in covariates was evaluated. Univariate exclusion of concomitant predictors had little to no impact on the point estimates of other covariates, indicating that the model provided unique information about each predictor.

The model for the age-related maturational effect on Cl was implemented as an asymptotically increasing maximum effect model. The model-estimated age at which 50% of full Cl was achieved was 1.53 months (54.7% SE). Given this point estimate, however, it is expected that 90% of full maturation Cl should occur at approximately 15 months. The model predicted a 10% increase in Cl for idiopathic PSF and a 3% reduction in Cl for non-idiopathic PSF as compared with the craniofacial group, neither of which is clinically relevant.

Observed *vs* population and individual predicted values revealed no systematic bias in the prediction of plasma

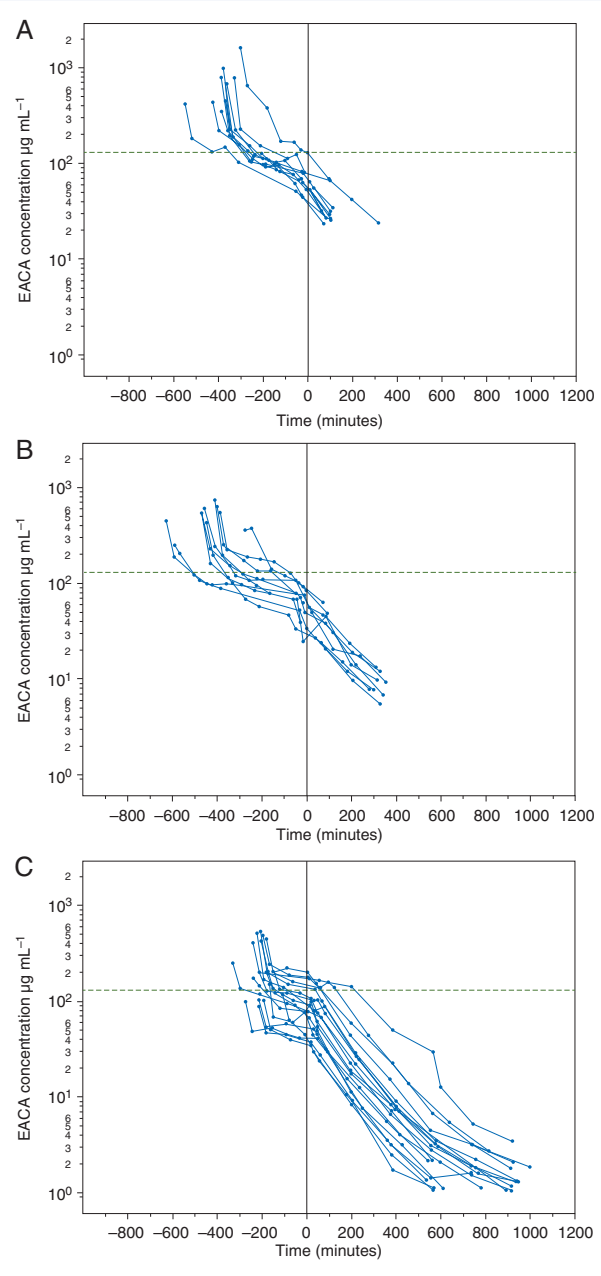

Fig 1 Semi-logarithmic concentration–time plots of EACA for populations with idiopathic scoliosis (panel A), non-idiopathic scoliosis (panel B) and craniofacial surgery (panel C). Note that the scoliosis population received a bolus of 100 mg kg^{-1} followed by a CIVI of 10 mg kg^{-1} h^{-1}. The craniofacial population was divided into three cohorts: 25 mg kg^{-1} loading with a CIVI of 10 mg kg^{-1} h^{-1}, 50 mg kg^{-1} loading with a CIVI of 20 mg kg^{-1} h^{-1}, and 100 mg kg^{-1} loading with a CIVI of 40 mg kg^{-1} h^{-1}. The horizontal dashed line indicates the target concentration of 130 mg litre^{-1}. Pre-bolus concentrations are omitted (all less than the lower limit of quantitation). Plasma concentrations obtained prior to and after end of infusion (time 0) are shown.

concentrations for the entire study (Fig. 2). Modelling progression is represented in Table 4. Age was a covariate of interest, and the age effect on clearance was included in the final model. However, given the small change in the MVOF, a model without age effect is also included. Parameter estimates for both models are represented in Table 5.

Dosing guidance

The population value for Cl was 153 ml min^{-1} 70 kg^{-1} and the allometric model was used to calculate Cl across a broad range of weights. For an infusion of 10 mg kg^{-1} h^{-1} as used in the PSF subjects, concentration at steady state was calculated assuming full maturation at 15 months (Table 6). This is graphically represented in Figure 3.

Weight-based dosing strategies that would result in a C_{ss} above the 97.5th prediction interval are presented in Table 7. Dosing strategies for patients <6 months of age are not provided, as the youngest child in this cohort was 6.7 months. Based on the population model, children weighing 7.5–24.9 kg should receive a CIVI of 40 mg kg^{-1} h^{-1} for >95% of the population to have a C_{ss} >130 mcg ml^{-1}, children weighing 25–49.9 kg should receive infusions of 35 mg kg^{-1} h^{-1}, and children weighing ≥50 kg should receive 30 mg kg^{-1} h^{-1} to achieve the same goals. A loading dose of 100 mg kg^{-1} is recommended for all patient weight groups.

Simulated concentration–time profiles for each cohort are presented in Figure 4. This simulation represents the best estimate of the range of concentrations using the specified dosing regimens without including the precision estimate of interindividual variability. The current dosing scheme (100 mg kg^{-1} load, 10 mg kg^{-1} h^{-1} CIVI) used in the scoliosis population does not result in concentrations >130 mcg ml^{-1} in any cohort once steady state is obtained. The large bolus dose:infusion dose ratio (10:1) provides higher concentrations initially, however, these concentrations cannot be maintained with a low CIVI dose. The minimal difference in the Cl parameter estimates for the idiopathic and non-idiopathic scoliosis subjects is demonstrated in the simulations (Fig. 4), where the simulated concentrations in the non-idiopathic group are almost identical to those in the idiopathic group using the same dosing regimen.

Discussion

Population PK parameters for EACA were estimated using a two-compartment disposition model with allometrically scaled weight and an age effect on clearance. Weight was referenced to 70 kg. Pharmacokinetic parameters for the typical patient were pre-/postoperative plasma drug clearance of 153 ml min^{-1} 70 kg^{-1} (6.32 ml min^{-1} kg$^{-0.75}$), intercompartmental clearance of 200 ml min^{-1} 70 kg^{-1} (8.26 ml min^{-1} kg$^{-0.75}$), central volume of distribution of 8.78 litre 70 kg^{-1} (0.13 litre kg^{-1}), and peripheral volume of distribution of 15.8 litre 70 kg^{-1} (0.23 litre kg^{-1}). An age effect on Cl remained after accounting for weight and was poorly estimated, as demonstrated by the per cent SE. Maturation of Cl was described with a half-maximal capacity by approximately 1.53 months and full maturation by 15 months. There was no clinically relevant impact of surgery type (PSF compared with craniofacial

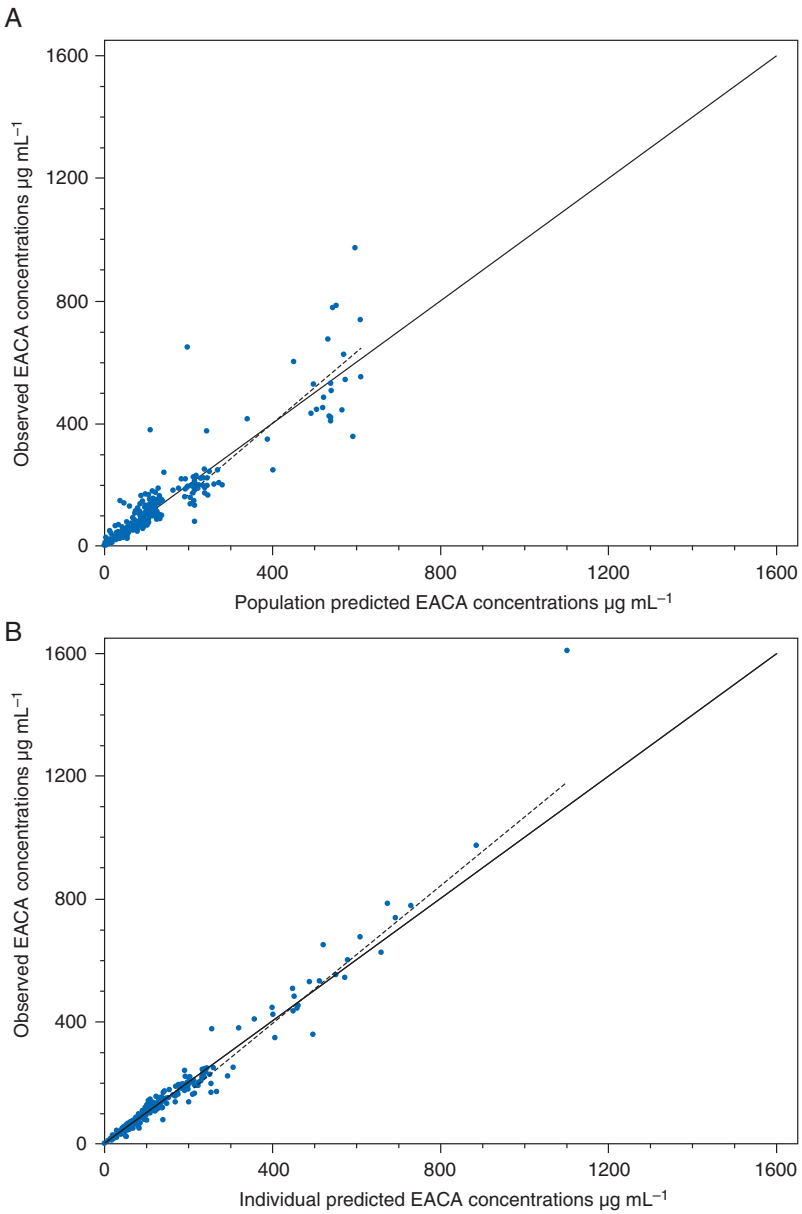

Fig 2 Observed *vs* population (panel A) and individual (panel B) predicted concentrations for the full model. A loess smoother is represented by the dashed line.

Table 4 Key modelling steps in the development of the full pharmacokinetic model. Final model is from run 105. MOFV, minimum objective function value; AIC, Akaike Information Criterion; IIV, interindividual variability. Bold type indicates the run used for the final model

Run	Reference run	Comments	MOFV	Change in MOFV	Number of parameters	AIC	Execution of covariance step
101		No weight, IIV on Cl and V1	2322.00		9	2340	Y
102	101	Added weight allometrically	2168.70	−153.30	9	2186.696	N
103	102	Added age	2167.41	−1.29	10	2187.407	Y
104	103	Added surgery type	2167.21	−0.20	11	2189.212	Y
105	104	Added IIV on V2 blocked	2095.98	−71.24	15	**2125.975**	Y
106	105	Added IIV on Q blocked	2086.76	−9.21	19	2124.762	Y
107	105	Added IIV on Q not blocked	2095.95	−0.02	16	2127.954	Y

Table 5 Parameter estimates from the weight-normalized EACA population pharmacokinetic models. SE%=(standard error/parameter estimate)*100. Interindividual variability=(square root of variance)*100. Covariance between Cl and V1 random effects was 0.074 (58% SE). Covariance between Cl and V2 random effects was 0.052 (65% SE). Covariance between V1 and V2 random effects was 0.064 (85% SE). $Cl=\theta^{*}_{Cl}(WT/70)^{0.75^{*}}(age/(1.53+age))*1.1$ (for idiopathic spines)*0.97 (for non-idiopathic spines). $V1=\theta^{*}_{V1}(WT/70)^{1}$. $Q=\theta^{*}_{Q}(WT/70)^{0.75}$. $V2=\theta^{*}_{V2}(WT/70)^{1}$

	Final model		Model without age effect	
Parameter	**Estimate**	**SE, %**	**Estimate**	**SE, %**
Cl, ml min^{-1} 70 kg^{-1}	153	7.51	133	5.69
V1, litres 70 kg^{-1}	8.78	10.01	8.8	9.9
Q, ml min^{-1} 70 kg^{-1}	199	11.31	199	11.2
V2, litres 70 kg^{-1}	15.80	6.33	15.8	6.39
Age Cl 50%, months	1.53	50.71	NA	NA
Impact of idiopathic spines	1.10	9.82	1.26	9.44
Impact of non-idiopathic spines	0.97	6.80	1.11	5.94
Parameter	Interindividual variability	SE, %	Interindividual variability	SE, %
ω^2_{Cl}	23.81	43.39	24.23	42.25
ω^2_{V1}	49.90	43.78	49.90	43.78
ω^2_{V2}	28.65	48.60	28.75	48.31
Residual variability	Variance	SE, %		
$\sigma^2_{proportional}$	0.026	18.31	0.026	18.1
$\sigma^2_{additive}$	0.673	20.65	0.676	20.9

Table 6 Predicted EACA steady-state concentrations (C_{ss}) using a linear weight-based dosing strategy at the lower 2.5th quantile of C_{ss} based on the allometrically derived clearance (Cl) estimate for individual weights with an EACA continuous infusion rate of 10 mg kg^{-1} h^{-1}. The target concentration is 130 mg $litre^{-1}$. Based on these estimates, an infusion of 10 mg kg^{-1} h^{-1} does not achieve a C_{ss} of 130 mg $litre^{-1}$ at the lower bound of the 95th prediction interval

Infusion dose, mg kg^{-1} h^{-1}	Weight, kg	Total dose, mg h^{-1}	Calculated Cl, litres h^{-1}	Calculated C_{ss}, mg $litre^{-1}$
10	10	100	2.09	47.8
10	15	150	2.83	52.9
10	20	200	3.52	56.8
10	25	250	4.16	60.1
10	30	300	4.77	62.9
10	35	350	5.35	65.4
10	40	400	5.92	67.6
10	45	450	6.46	69.6
10	50	500	6.99	71.5
10	55	550	7.51	73.2
10	60	600	8.02	74.8
10	65	650	8.51	76.3
10	70	700	9.00	77.7
10	75	750	9.48	79.1
10	80	800	9.95	80.4

surgery) or of PSF study group (idiopathic compared with non-idiopathic) on drug Cl.

Many biologic characteristics are described using allometric scaling, where the observed characteristic exhibits a logarithmic relationship with weight or size rather than a linear relationship. As a result of this logarithmic relationship in the PKs of EACA, if linear dosing is used, a 15 kg difference in weight in children (e.g. 25 kg *vs* 10 kg) will have a disproportionately higher effect on drug concentrations compared with the same 15 kg difference in an adult (e.g. 85 kg *vs* 70 kg). Consequently, interpolating paediatric dosing from adult dosing in a linear fashion based on weight is problematic and often results in subtherapeutic or supratherapeutic drug concentrations. This was seen in Figure 3, where a fixed dosing strategy results in a lower C_{ss} for a 10 kg patient *vs* a 50 kg patient.

The therapeutic plasma concentration of EACA to control systemic fibrinolytic activity was determined to be 130 mcg mL^{-1}; dosing strategies based on PK studies in adults[10 12] and children[22] have been targeted to maintain plasma EACA levels of $\geq$130 mg $litre^{-1}$ (1 mM).[20 21] This target plasma concentration of EACA is based on *in vitro* data where the therapeutic concentration is the concentration that completely inhibits fibrinolysis caused by supraphysiologic plasminogen activation. There is currently no suitable pharmacodynamic indicator for determining target EACA concentrations for blood loss reduction in non-cardiac surgery. In a study evaluating the antifibrinolytic tranexamic acid in craniofacial surgery, efficacy in reducing blood loss was demonstrated without a detectable effect on fibrinolytic activity on thromboelastography for tranexamic acid.[23] Given the absence of EACA dose or concentration range efficacy data in this population, therapeutic targets remain based on *in vitro* data.[24] The evidence for adverse effects of slight overdosing of EACA is sparse. Going forth, a trial to determine the minimal concentration for efficacy as well as whether a larger concentration might prove more efficacious is needed.

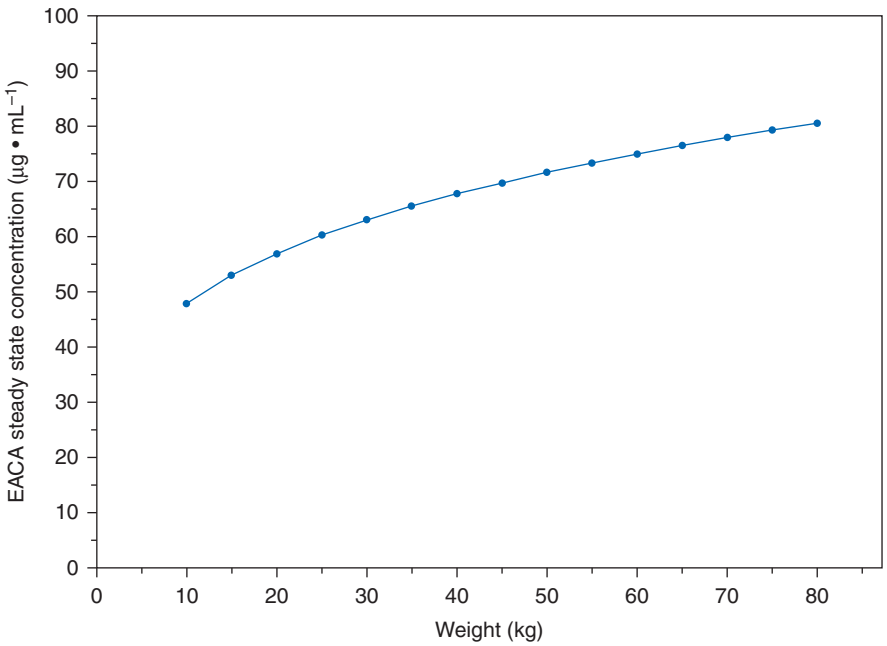

Fig 3 Steady-state EACA concentrations achieved using an infusion of 10 mg kg^{-1} h^{-1} for different weights assuming full maturation as seen after 15 months.

Table 7 Predicted EACA steady-state concentrations (C_{ss}) using a linear weight-based dosing strategy to achieve a C_{ss} of 130 mg $litre^{-1}$ at the lower 2.5th quantile of C_{ss} based on the allometrically derived clearance (Cl) estimate for individual weights and ages. *Indicates age adjusted Cl. Based on calculations, the following continuous infusion rates are recommended according to patient weight: weight <25 kg, 40 mg kg^{-1} h^{-1}; weight ≤25–<50 kg, 35 mg kg^{-1} h^{-1}; weight ≥50 kg, 30 mg kg^{-1} h^{-1}

Weight, kg	Age, months	Dose, mg kg^{-1} h^{-1}	Dose rate, mg h^{-1}	Cl, litres h^{-1}	C_{ss}, mg $litre^{-1}$
7.5	6	40	300	2.18*	137
8.4	9	40	336	2.55*	131
9.5	12	40	380	2.90*	130
10.4	15	40	416	3.18*	130
12	—	40	480	3.90	123
15	—	40	600	4.61	130
25	—	35	875	6.76	129
35	—	35	1225	8.70	140
40	—	35	1400	9.62	145
50	—	30	1500	11.37	131
60	—	30	1800	13.04	138
70	—	30	2100	14.64	143

Limitations

Although sample size was a potential limitation of this study, the structural PK parameters were precisely estimated. Previous PK studies of EACA in adults have included 6 subjects,[11] 10 subjects,[25] and 16 subjects.[26] PK studies in children involved 9 subjects[22] and 18 subjects.[15] Another limitation was that there were fewer postoperative PK samples collected. However, initial postoperative samples (0.5 and 2 h following the end of the CIVI) were collected in nearly all subjects, and all potential intraoperative samples were drawn in all subjects. The current study did not provide reliable information about the effects of age. Although the estimate of age effect was imprecise, it was included in the final model since it represents a clinically relevant covariate.

Conclusions

EACA PK behaviour is influenced by weight, age and perioperative conditions (intraoperative compared with postoperative time period). Weight-based dosing in this population is appropriate, and based on modelling from this study, the following dosing schemes are recommended to maintain target plasma EACA concentrations: weight <25 kg, 100 mg kg^{-1} loading dose and 40 mg kg^{-1} h^{-1} infusion; weight ≤25–<50 kg, 100 mg kg^{-1} loading dose and 35 mg kg^{-1} h^{-1} infusion; weight ≥50 kg, 100 mg kg^{-1} loading dose and 30 mg kg^{-1} h^{-1} infusion. The recommended infusion rate is at least three times what has been used in prior EACA efficacy studies conducted in adolescents undergoing PSF. A prospective trial using the dosing recommendations from this study evaluating the efficacy of EACA in this population is warranted. It is possible that such a trial would demonstrate greater efficacy of EACA than previously reported.

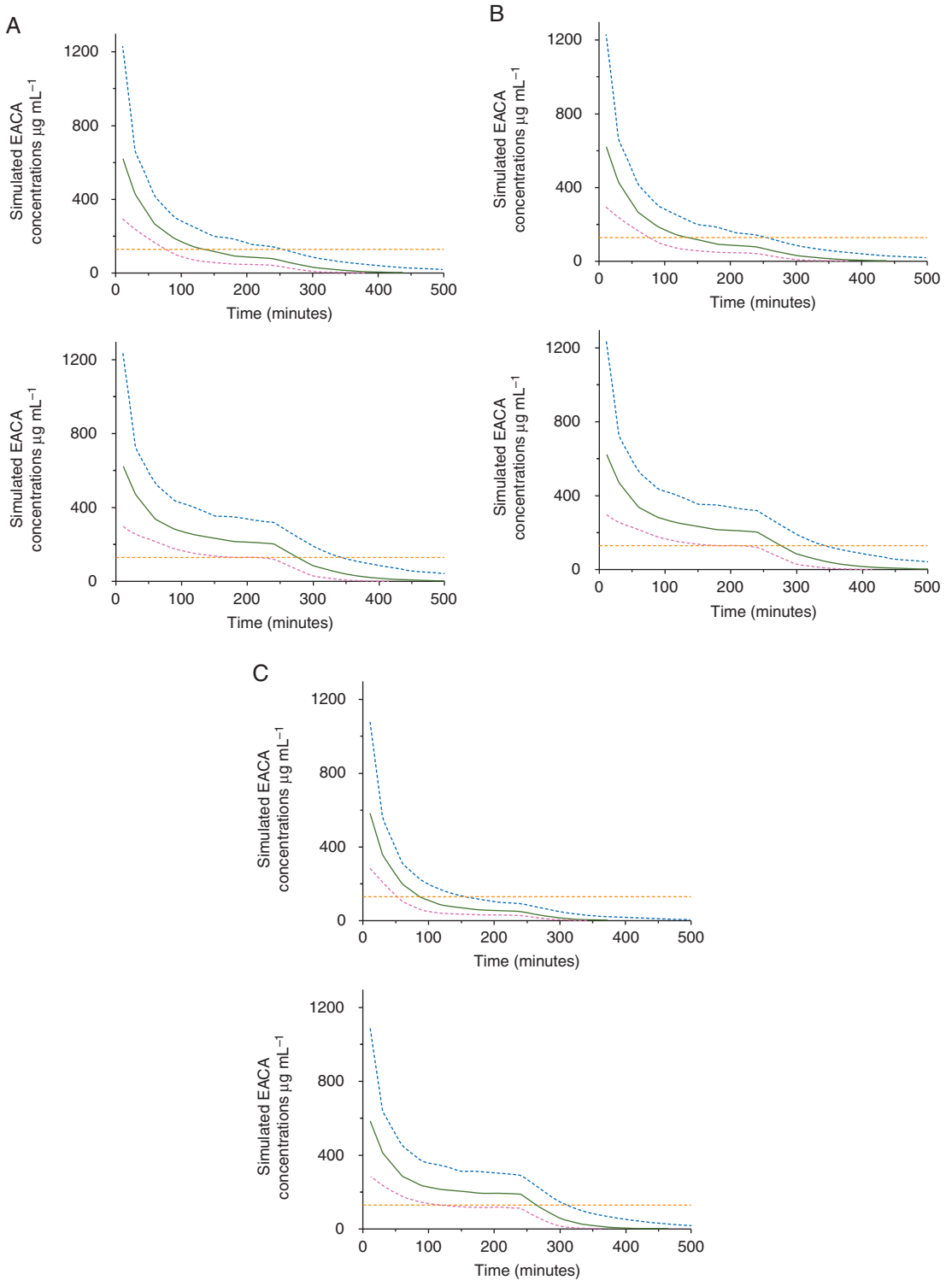

Fig 4 Simulated concentration–time profiles. (A). Simulated concentration–time profile for a population of children with idiopathic scoliosis (typical weight 55 kg, age 187.5 months) who received either the dosing regimen used in the study, 100 mg kg^{-1} bolus over 10 min followed by a CIVI of 10 mg kg^{-1} h^{-1} for 4 h (top panel), or 100 mg kg^{-1} over 10 min followed by a CIVI of 30 mg kg^{-1} h^{-1} (bottom panel). (B) Simulated concentration–time profile for a population of children with non-idiopathic scoliosis (typical weight 33.7 kg, age 165 months). Same dosing regimens as in (A). (C) Simulated concentration–time profile for a population of children undergoing craniofacial surgery (typical weight 8.8 kg, age 38 weeks) who received either 100 mg kg^{-1} bolus over 10 min followed by a CIVI of 10 mg kg^{-1} h^{-1} for 4 h (top panel) or 100 mg kg^{-1} over 10 min followed by a CIVI of 40 mg kg^{-1} h^{-1} (bottom panel). Dashed lines represent 2.5th and 97.5th quantiles of the population variability interval while the solid line represents the median. Pink line represents the target concentration of 130 mg $litre^{-1}$.

Author's contributions

P.A.S.: study design, conduct of study, data collection, data analysis, manuscript preparation. M.R.G.: data analysis, manuscript preparation. D.S. and J.E.F.: study design, conduct of study, manuscript preparation. E.S., E.Y.P., and T.K.G.: conduct of study, data collection. A.F.Z.: study design, conduct of study, data analysis, manuscript preparation.

Acknowledgements

The authors wish to acknowledge and thank Ganesh Moorthy, PhD, who performed the EACA assays.

Declaration of interest

None declared.

Funding

This work was funded in part by the National Institutes of Health/National Center for Research Resources (UL1-RR-0204134).

References

1 Thompson GH, Florentino-Pineda I, Poe-Kochert C, Armstrong DG, Son-Hing J. Role of amicar in surgery for neuromuscular scoliosis. *Spine (Phila Pa 1976)* 2008; **33**: 2623–9

2 Florentino-Pineda I, Thompson GH, Poe-Kochert C, Huang RP, Haber LL, Blakemore LC. The effect of amicar on perioperative blood loss in idiopathic scoliosis: the results of a prospective, randomized, double-blind study. *Spine* 2004; **29**: 233–8

3 Verma K, Errico T, Diefenbach C, *et al.* The relative efficacy of antifibrinolytics in adolescent idiopathic scoliosis: a prospective randomized trial. *J Bone Joint Surg* 2014; **96**: e80

4 Dhawale AA, Shah SA, Sponseller PD, *et al.* Are antifibrinolytics helpful in decreasing blood loss and transfusions during spinal fusion surgery in children with cerebral palsy scoliosis? *Spine (Phila Pa 1976)* 2012; **37**: E549–55

5 Florentino-Pineda I, Blakemore LC, Thompson GH, Poe-Kochert C, Adler P, Tripi P. The effect of epsilon-aminocaproic acid on perioperative blood loss in patients with idiopathic scoliosis undergoing posterior spinal fusion. *Spine (Phila Pa 1976)* 2001; **26**: 1147–51

6 Thompson GH, Florentino-Pineda I, Armstrong DG, Poe-Kochert C. Fibrinogen levels following amicar in surgery for idiopathic scoliosis. *Spine (Phila Pa 1976)* 2007; **32**: 368–72

7 Thompson GH, Florentino-Pineda I, Poe-Kochert C. The role of amicar in decreasing perioperative blood loss in idiopathic scoliosis. *Spine (Phila Pa 1976)* 2005; **30**: S94–S9

8 Thompson GH, Florentino-Pineda I, Poe-Kochert C, Armstrong DG, Son-Hing JP. The role of amicar in same-day anterior and posterior spinal fusion for idiopathic scoliosis. *Spine (Phila Pa 1976)* 2008; **33**: 2237–42

9 Nilsson IM, Sjoerdsma A, Waldenstrom J. Antifibrinolytic activity and metabolism of 6-aminocaproic acid in man. *Lancet* 1960; **1**: 1322–6

10 Bennett-Guerrero E, Sorohan JG, Canada AT, *et al.* Epsilon-aminocaproic acid plasma levels during cardiopulmonary bypass. *Anesth Analg* 1997; **85**: 248–51

11 Frederiksen MC, Bowsher DJ, Ruo TI, Henthorn CT, Green D, Atkinson AJ. Kinetics of epsilon-aminocaproic acid distribution, elimination, and antifibrinolytic effects in normal subjects. *Clin Pharmacol Ther* 1984; **35**: 387–93

12 Butterworth J, James RL, Lin Y, Prielipp RC, Hudspeth AS. Pharmacokinetics of epsilon-aminocaproic acid in patients undergoing aortocoronary bypass surgery. *Anesthesiology* 1999; **90**: 1624–35

13 Butterworth J, James RL, Lin YA, Bennett J, Prielipp RC. Gender does not influence epsilon-aminocaproic acid concentrations in adults undergoing cardiopulmonary bypass. *Anesth Analg* 2001; **92**: 1384–90

14 Fish SS, Pancorbo S, Berkseth R. Pharmacokinetics of epsilon-aminocaproic acid during peritoneal dialysis. *J Neurosurg* 1981; **54**: 736–9

15 Stricker PA, Zuppa AF, Fiadjoe JE, *et al.* Population pharmacokinetics of epsilon-aminocaproic acid in infants undergoing craniofacial reconstruction surgery. *Br J Anaesth* 2013; **110**: 788–99

16 Anderson BJ, McKee AD, Holford NH. Size, myths and the clinical pharmacokinetics of analgesia in paediatric patients. *Clin Pharmacokinet* 1997; **33**: 313–27

17 West GB, Brown JH, Enquist BJ. The fourth dimension of life: fractal geometry and allometric scaling of organisms. *Science* 1999; **284**: 1677–9

18 Harrell F. *Regression Modeling Strategies*. New York: Springer-Verlag, 2001

19 Ribbing J, Jonsson EN. Power, selection bias and predictive performance of the population pharmacokinetic covariate model. *J Pharmacokinet Pharmacodyn* 2004; **31**: 109–34

20 Alkjaersig N, Fletcher AP, Sherry S. Epsilon-aminocaproic acid: an inhibitor of plasminogen activation. *J Biol Chem* 1959; **234**: 832–7

21 Ablondi FB, Hagan JJ, Philips M, DeRenzo EC. Inhibition of plasmin, trypsin, and the streptokinase-activated fibrinolytic system by epsilon-aminocaproic acid. *Arch Biochem Biophys* 1959; **82**: 153–60

22 Ririe DG, James RL, O'Brien JJ, *et al.* The pharmacokinetics of epsilon-aminocaproic acid in children undergoing surgical repair of congenital heart defects. *Anesth Analg* 2002; **94**: 44–9

23 Goobie SM, Meier PM, Pereira LM, *et al.* Efficacy of tranexamic acid in pediatric craniosynostosis surgery: a double-blind, placebo-controlled trial. *Anesthesiology* 2011; **114**: 862–71

24 Nielsen VG, Cankovic L, Steenwyk BL. Epsilon-aminocaproic acid inhibition of fibrinolysis in vitro: should the 'therapeutic' concentration be reconsidered? *Blood Coagul Fibrinolysis* 2007; **18**: 35–9

25 Dvorchik BH, Katlic KL, Hayes AH Jr, Eyster ME. Effect of probenecid on the kinetics of epsilon-aminocaproic acid. *Clin Pharmacol Ther* 1980; **28**: 223–8

26 McNicol G, Fletcher A, Alkjaersig N, Sherry S. The absorption, distribution, and excretion of epsilon-aminocaproic acid following oral or intravenous administration to man. *J Lab Clin Med* 1962; **59**: 15–24

Handling editor: H. C. Hemmings