A Practical Tranexamic Acid Dosing Scheme Based on Population Pharmacokinetics in Children Undergoing Cardiac Surgery

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Abstract

Background: Pediatric cardiac surgery patients are at high risk for bleeding, and the antifibrinolytic drug tranexamic acid (TA) is often used to reduce blood loss. However, dosing schemes remain empirical as a consequence of the absence of pharmacokinetic study in this population. The authors’ objectives were thus to investigate the population pharmacokinetics of TA in pediatric cardiac surgery patients during cardiopulmonary bypass (CPB).

Methods: Twenty-one patients were randomized to receive TA either continuously (10 mg/kg followed by an infusion of 1 mg·kg⁻¹·h⁻¹ throughout the operation, and 10 mg/kg into the CPB) or discontinuously (10 mg/kg into the CPB and 10 mg·kg⁻¹·h⁻¹ at the end of CPB). Serum concentrations were measured at eight time points with chromatography–mass spectrometry and the data were modeled using Monolix (Lixoft, Orsay, France).

Results: Tranexamic acid pharmacokinetics was ascribed to a two-compartment open model. The main covariate effects were body weight and CPB. Representative pharmacokinetic parameters adjusted to a 70-kg body weight were as follows: systemic clearance, 2.45 l/h; volume of distribution in the central compartment, 14.1 l; intercompartmental clearance, 5.74 l/h; and peripheral volume, 32.8 l. In accordance with this model, the authors proposed a weight-adjusted dosing scheme to maintain effective TA concentrations in children during surgery, consisting of one loading dose followed by a continuous infusion.

Conclusions: The authors report for the first time the pharmacokinetics of TA in children undergoing cardiac surgery with CPB, and propose a dosing scheme for optimized TA administration in those children.

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Address correspondence to Dr. Grassin-Delyle: Laboratoire de Pharmacologie, UPRES EA220, Hôpital Foch, Suresnes, France. s.grassindelyle@hopital-foch.org. 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. Copyright © 2013, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins. Anesthesiology 2013; 118:853–62

PEDIATRIC cardiac surgery patients are at high risk for bleeding, in part because of the cardiopulmonary bypass (CPB) circuits that activate coagulation, inflammatory, and fibrinolytic systems.1–3 Bleeding is more common than in adults, exposing children to all the risks associated with allogenic transfusions.4 The use of antifibrinolytic drugs is one of the strategies for reducing blood loss, and tranexamic acid (TA) is among the most commonly administered, especially because the conclusions of the Blood Conservation Using Antifibrinolytics in a Randomized Trial study raised concerns about aprotinin.5 The efficacy of TA in pediatric cardiac surgery has been demonstrated in several trials6–11 and analyses,12,13 but the determination of its dosage regimen

What We Already Know about This Topic

• Bleeding in pediatric cardiac surgery patients is more common than in adults, exposing children to the risks associated with allogenic transfusions. Although the efficacy of tranexamic acid in pediatric cardiac surgery has been previously demonstrated, pharmacokinetic analysis of the optimal dosing regimen remains lacking.

• This study investigated the population pharmacokinetics of tranexamic acid in pediatric cardiac surgery patients undergoing cardiopulmonary bypass.

What This Article Tells Us That Is New

• The population pharmacokinetics and a proposed dosing scheme for optimized tranexamic acid administration in children undergoing cardiac surgery with cardiopulmonary bypass is described.
in such trials was empirical as a consequence of the absence of pharmacokinetic analysis in the pediatric population.

Even if a unique dose was sometimes administered before skin incision,7,11,14 dosing schemes were usually based on a loading dose before incision and another dose in the CPB prime volume, in combination with a continuous infusion throughout surgery7,9,10 or with another bolus at the end of CPB.6–8,15 In addition, a significant variability between practitioners may be observed for each of those doses, as already illustrated with a 10-fold factor in the total dose (i.e., dose ranging from 30–300 mg/kg).6,8 Some dosing schemes have been inspired from pharmacokinetic data in adults,16 but the relevance of such an extrapolation may be questioned, because differences in the pharmacokinetics between adults and children undergoing cardiac surgery with CPB have already been reported.17,18 Moreover, the prime volume for CPB in infants represents approximately 50–100% of their blood volume and is therefore responsible for an additional impairment of hemostasis related to dilutional effects, which may also affect the pharmacokinetics of antifibrinolytic drugs.2,19

The lack of pharmacokinetic/pharmacodynamic data reinforces the difficulties of determining the best dosage regimen for TA in children. The effective in vivo concentrations remain unknown, but a target TA plasma concentration of 20 µg/ml has been suggested for patients undergoing CPB16 on the basis of in vitro studies that showed a suppression of fibrinolytic activity with 10 µg/ml TA and suppression of plasmin-induced platelet activation with 16 µg/ml TA.20,21

Altogether, rational evidence for determining the best scheme remains sparse. Because drug doses should be determined on the basis of pharmacokinetic analysis in the desired population rather than by empirical approaches, the objectives of our study were to perform such an analysis for the first time in pediatric surgery patients and to propose a dosing scheme that would allow the maintenance of effective blood concentrations throughout surgery.

Materials and Methods

Clinical Protocol

After institutional review board (Comité de Protection des Personnes Île de France VII, Hôpital de Bicêtre, Le Kremlin Bicêtre, France) approval and written informed consent from both parents had been obtained, 21 children with an American Society of Anesthesiologists physical status of III were enrolled. The study was prospective and randomized, and identified at clinicaltrials.gov under the reference NCT01141127. Inclusion criteria were congenital heart disease requiring cardiac surgery by sternotomy with CPB in children aged 12 months to 12 years and weighing between 10 and 30 kg. Randomization was stratified on the basis of the children's weight, and three groups were considered: 10 to <15, 15 to <20, and 20–30 kg. Children were assigned into one of the two treatment groups: the continuous TA group received a loading dose of 10 mg/kg TA (Exacyl; Sanofi-Aventis, Paris, France) IV over 5 min, followed by an infusion of 1 mg·kg⁻¹·h⁻¹ throughout the operation, and 10 mg/kg into the CPB prime volume. The discontinuous TA group received a loading dose of TA 10 mg/kg over 5 min, followed by 10 mg/kg into the CPB prime volume and 10 mg/kg at the end of CPB. Excluded were patients with preexisting hemostasis anomaly, renal insufficiency, or known allergy to TA. Anesthesia, anticoagulation, and surgical technique were in accordance with the standard hospital protocol. Anesthesia was performed with sufentanil–benzodiazepine or propofol combination and pancuronium neuromuscular blockade. CPB was performed in normothermia (35.4°–37°C) at a flow rate of 2.4 l·min⁻¹·m⁻² without ultrafiltration. Two types of CPB systems were used, either Kids D101 (Sorin Group, Milan, Italy) or Capiox Baby FX (Terumo, Guyancourt, France). A crystalloid priming volume was used, or a mixture of blood and plasma was added to the pump prime if the calculated initial hemoglobin on CPB based on the prime volume and the hemoglobin measured in the operating room was estimated to be less than 10 g/dl. Prime volumes were 300–330 ml for children weighing between 10 and 15 kg, 450–650 ml for children weighing between 15 and 25 kg, and 650–750 ml for children weighing between 25 and 30 kg (one 30-kg child received 1,070 ml). Unfractioned heparin was given at 300 U/kg plus 5,000 U/I in the CPB prime volume, and additional heparin was given to maintain an activated coagulation time greater than 400 s. Neutralization was ensured by protamine at the dose of 3 mg/kg. Crystalloid solution, plasma, or blood was administered during CPB, and additional blood or blood products were administered after CPB as needed. The criteria for blood transfusion was to maintain hemoglobin greater than 10 g/dl.

Sample Acquisition, Handling, and Processing

A set of eight arterial blood samples (3 ml) were collected in sampling tubes without anticoagulant or polymer gel at the following nominal times: predose (baseline), 10 min after the loading dose, before CPB initiation, 30 and 60 min after the beginning of CPB, at the end of CPB, 10 min after the end of CPB, and at the end of surgery. Serum was separated by centrifugation (4000 g for 10 min at 4°C) and stored at −80°C until analysis.

TA Assay

Analysis of TA serum concentrations was performed using liquid chromatography coupled with mass spectrometric detection, according to a fully validated and previously described procedure.22 Intraday and interday coefficients of variation were less than or equal to 8.1 and 9.7%, respectively, with intraday and interday accuracies ranging from 93.2–100.5%. Serum samples (100 µl) were subjected to acidic protein precipitation with perchloric acid. After pH adjustment, chromatography was performed on a C₁₈ column and compounds were detected with an ion-trap mass spectrometer. The method was linear, accurate, and precise in the range 1.0 (used as limit of quantification) to 200 µg/ml.
Pharmacokinetic Modeling

A two-compartment open model was first fitted to TA data:

\[
\frac{dA_1}{dt} = -k_{10} \times A_1 - k_{12} \times A_1 + k_{21} \times A_2
\]

(1)

\[
\frac{dA_2}{dt} = k_{12} \times A_1 - k_{21} \times A_2
\]

(2)

where \( k_{10} \) = elimination clearance (CL)/volume of the central compartment (Vc), \( k_{12} = \) intercompartmental clearance (Q)/Vc, and \( k_{21} \) = Q/volume of the peripheral compartment (Vp). A parameter relating the CPB to a modification of any of the pharmacokinetic parameters (\( \theta_{\text{CPB}} \)) was included in the model as follows:

\[
P = P_{\text{TYPICAL}} \left( \frac{V_{\text{CPB}}}{500} \right)^{\Omega_{\text{CPB}}}
\]

(3)

where \( P \) denotes a clearance or volume term, \( P_{\text{TYPICAL}} \) is the typical parameter value, and \( V_{\text{CPB}} \) is the CPB prime volume. This was applied from the start to the end of the CPB procedure.

Statistical Analysis

Data were analyzed using the nonlinear mixed effect modeling software program Monolix (Lixoft, Orsay, France) version 3.2.23–25 Parameters were estimated by computing the maximum likelihood estimator of the parameters without any approximation of the model (no linearization) using the stochastic approximation expectation maximization algorithm combined with a Markov chain Monte Carlo procedure. A proportional error model was used to describe the residual variability (\( \varepsilon_{\text{PROP}} \)), and the between-subject variabilities (BSV or \( \eta \)) were ascribed to an exponential error model. Parameter shrinkage was calculated as 1 – SD(\( \eta \))/\( \omega \), where SD(\( \eta \)) and \( \omega \) are the SD of individual \( \eta \) parameters and the population model estimate of the BSV, respectively. The likelihood ratio test including the log-likelihood and the Bayesian information criterion was used to test different hypotheses regarding the final model, covariate effect on pharmacokinetic parameter(s), residual variability model (proportional vs. proportional plus additive error model), and structure of the variance–covariance matrix for the BSV parameters. Diagnostic graphics and other statistics were obtained using the R program.26 From the final model, 500 simulations were performed to compute the normalized prediction distribution error metrics, whose mean, variance, and distribution must not be different from 0, 1, and a normal distribution, respectively.27

Results

Population Characteristics and TA Concentrations

The demographic characteristics and CPB details are listed in table 1. Abnormalities, types of surgery, and blood loss are listed in table 2. There were no differences between the two groups. Twelve blood samples (of 168) were missing because of CPB durations less than 60 min (five in the continuous group and seven in the discontinuous group), and five other samples (two in the continuous group and three in the discontinuous group), all at the same time point (10 min after the end of CPB). In the continuous group, TA concentrations during surgery were in the range 8.1–91.1 \( \mu \)g/ml, with nine values (16.1% of the total available values) lower than 20 \( \mu \)g/ml well distributed over the different time points. In the discontinuous group, TA concentrations were between 7.7 and 106.7 \( \mu \)g/ml, with 12 values (16.2% of the total available values) lower than 20 \( \mu \)g/ml, 11 of which were for the sample taken just before CPB initiation.

Population Pharmacokinetic Modeling

Pharmacokinetic time courses were best described by a two-compartment open model. The parameters of the model were then CL and Q, and Vc and Vp. BSVs were estimated for all structural parameters except Vp. Residual variability was described by a proportional error model. At this step, CL was 0.68 l/h (relative standard error, 37%) and the corresponding BSV was 0.73 (relative standard error, 31%).

The main covariate effects were body size effects and the CPB. Table 3 summarizes the model-building steps for the body size effects. The pharmacokinetic parameters were allo-metrically normalized for body weight (BW) to a 70-kg individual as follows:

\[
P_r = P_{\text{TYPICAL}} \left( \frac{\text{BW}}{70} \right)^{\Omega_{\text{NORM}}}
\]

(4)

Table 1. Subject and Cardiopulmonary Bypass Characteristics

<table>
<thead>
<tr>
<th>Continuous</th>
<th>Discontinuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>9</td>
</tr>
<tr>
<td>F/M</td>
<td>6/3</td>
</tr>
<tr>
<td>Age, yr</td>
<td>5.0 ± 2.5</td>
</tr>
<tr>
<td>BW, kg</td>
<td>17.6 ± 5.9</td>
</tr>
<tr>
<td>Height, cm</td>
<td>103.9 ± 17.3</td>
</tr>
<tr>
<td>CPB priming volume, ml</td>
<td>418.9 ± 90.6</td>
</tr>
<tr>
<td>CPB priming liquid, No.</td>
<td></td>
</tr>
<tr>
<td>Cristalloid alone</td>
<td>5</td>
</tr>
<tr>
<td>Cristalloid plus blood</td>
<td>1</td>
</tr>
<tr>
<td>Cristalloid plus plasma</td>
<td>0</td>
</tr>
<tr>
<td>Cristalloid plus blood plus plasma</td>
<td>2</td>
</tr>
<tr>
<td>Blood plus plasma</td>
<td>1</td>
</tr>
<tr>
<td>CPB duration, min</td>
<td>76.7 ± 45.8</td>
</tr>
<tr>
<td>Surgery duration, min</td>
<td>255.0 ± 50.8</td>
</tr>
<tr>
<td>Preoperative creatinine clearance, ml/min</td>
<td>97.4 ± 11.9</td>
</tr>
</tbody>
</table>

Normally distributed data (as evaluated with the D’Agostino–Pearson normality test) are presented as mean ± SD. BW = body weight; CPB = cardiopulmonary bypass; F = female; M = male.
where i denotes the \( i^{th} \) individual. The power exponents were set to \( \frac{3}{4} \) and 1 for the clearance and volume terms, respectively. This significantly decreased the BSV estimate (BSV of CL decreased from 0.73 to 0.42) and improved the predictive performance of the model with a decrease of 5 units in Bayesian information criterion. The CPB had an effect on the intercompartmental clearance and involved a significant increase in the exchange dynamics. Figure 1 depicts the improvement of the predictive performance of the final model. The final covariate model was then:

\[
CL(1/h) = 2.45 \times (BW/i70)^{3/4} \\
Vc(l) = 14.1 \times (BW/i70)^{1/2} \\
Q(1/h) = 5.74 \times (BW/i70)^{3/4}
\]

Table 4 shows the final population pharmacokinetic estimates. Most of the parameters were well estimated, with low relative standard errors. The empirical Bayesian estimate shrinkages were low. The goodness-of-fit plots are depicted in figure 2, and figure 3 shows representative pharmacokinetic time courses.

### Simulation of TA Concentrations Obtained with Various Dosing Schemes

We used our pharmacokinetic model to simulate the TA concentrations that would be obtained in children with the various previously reported dosing schemes. Data were simulated for children between 5 and 40 kg, assuming a 4-h surgical procedure, 2 h between the first bolus dose and the CPB initiation, and a CPB duration of 70 min. As shown in figure 4, the schemes with two 20-mg/kg doses (fig. 4B), three 10-mg/kg doses (fig. 4C), or one 10-mg/kg bolus dose followed with a continuous 1-mg-h\(^{-1}\)-kg\(^{-1}\) infusion (fig. 4E) do not allow concentrations to be maintained above 20 µg/ml throughout the entire surgical procedure for all of the patients. In contrast, the schemes with a unique 50-mg/kg bolus dose (fig. 4A), three 100-mg/kg doses (fig. 4D), or two 50- (fig. 4F) or 100-mg/kg (fig. 4G) doses followed with a continuous 15- or 10-mg-h\(^{-1}\)-kg\(^{-1}\) infusions, respectively, allow this
threshold concentration to be maintained, but with variability in the 5- to 40-kg weight range, and above all with maximal TA concentrations that could reach up to nearly 700 µg/ml (fig. 4, D and F).

**Dosing Proposal**

From our pharmacokinetic modeling, we have determined the most appropriate dosing scheme to obtain a given target concentration in children weighing 5–40 kg. As an illustration, we assumed that a minimum therapeutic concentration of 20 µg/ml must be achieved or exceeded in all patients during surgery, as previously proposed by Dowd et al.16 Because the children's BW was the main covariate in our modeling, we proposed a weight-adjusted scheme (table 5). We found that for children undergoing cardiac surgery with CPB, a loading dose given in 5 min associated with a continuous infusion throughout surgery (without dosing in the CPB prime volume) should allow the target concentration to be maintained in all children (fig. 5). The recommended loading dose is identical for all children on a per-kilogram basis (6.4 mg/kg), whereas the infusion rate decreases with weight from 3.1 mg·h⁻¹·kg⁻¹ to 2.0 mg·h⁻¹·kg⁻¹ for children between 5 and 40 kg, respectively. As illustrated in figure 5, our proposal allows blood concentrations to be maintained between 20 and approximately 30 µg/ml at all time points, regardless of the children's BW. Importantly, because the

<table>
<thead>
<tr>
<th>Model</th>
<th>Details</th>
<th>BIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Two-compartment</td>
<td>CL, Vc, Q, Vp</td>
<td>990</td>
</tr>
<tr>
<td>B. (A) + effect of BW</td>
<td>CL or Q = P_TYPICAL × (BW/70)⁰.⁷⁵, Vc or Vp = P_TYPICAL × (BW/70)⁰.⁷⁵, Ση²(CL + Vc + Q) = 3.21</td>
<td>970</td>
</tr>
<tr>
<td>C. (B) + effect of CPB on Vp</td>
<td>Vp = P_TYPICAL × (VCPB/500)ᶜ⁰/ᶜ × (BW/70)⁰.⁷⁵, Ση²(CL + Vc + Q) = 1.08</td>
<td>975</td>
</tr>
<tr>
<td>D. (B) + effect of CPB on Vc</td>
<td>Vc = P_TYPICAL × (VCPB/500)ᶜ⁰/ᶜ × (BW/70)⁰.⁷⁵, Ση²(CL + Vc + Q) = 3.34</td>
<td>972</td>
</tr>
<tr>
<td>E. (B) + effect of CPB on CL</td>
<td>CL = P_TYPICAL × (VCPB/500)ᶜ⁰/ᶜ × (BW/70)⁰.⁷⁵, Ση²(CL + Vc + Q) = 1.30</td>
<td>966</td>
</tr>
<tr>
<td>F. (B) + effect of CPB on Q</td>
<td>Q = P_TYPICAL × (VCPB/500)ᶜ⁰/ᶜ × (BW/70)⁰.⁷⁵, Ση²(CL + Vc + Q) = 0.86</td>
<td>965</td>
</tr>
</tbody>
</table>

Ση²(CL + Vc + Q) denotes the sum of between subject variances (η²s) for the clearance and volume parameters. For all models, the residual variability was described as a proportional error model.

* Best model to fit the data.

BIC = Bayesian information criterion; BW = body weight (kg); CL = clearance; CPB = cardiopulmonary bypass; η = between-subject variability; P_TYPICAL = typical value of parameter; Q = intercompartmental clearance; Vc = volume of the central compartment; VCPB = CPB prime volume; Vp = volume of the peripheral compartment.

**Fig. 1.** Improvement of the predictive performance of the model from the basic (covariate-free) model (2 compartments base) to the final model: observed tranexamic acid concentrations vs. population model predictions. The solid, red, and blue lines denote the identity, actual regression, and spline function lines, respectively. TA = tranexamic acid.
pharmacokinetics is linear, if the desired target concentration should be multiplied (i.e., 50 instead of 20 µg/ml), the dose and rate should be multiplied by the same factor (i.e., 159 mg as a loading dose followed with a 67-mg/h infusion for a 10-kg child, instead of 64 mg and 27 mg/h, respectively, according to table 5).

### Table 4. Parameter Estimates of the Final Tranexamic Acid Population Model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Covariate Effect</th>
<th>Estimate (% RSE)</th>
<th>BSV (% RSE) [Shrinkage]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (l·h⁻¹·70 kg⁻¹)</td>
<td>(BW/70)⁰.⁷⁵</td>
<td>2.45 (36)</td>
<td>0.45 (37) [0.33]</td>
</tr>
<tr>
<td>Vc (l/70 kg)</td>
<td>(BW/70)¹</td>
<td>14.1 (7)</td>
<td>0.21 (33) [0.33]</td>
</tr>
<tr>
<td>Q (l·h⁻¹·70 kg⁻¹)</td>
<td>(BW/70)⁰.⁷⁵</td>
<td>5.74 (28)</td>
<td>0.80 (25) [0.26]</td>
</tr>
<tr>
<td>During CPB*</td>
<td>θ&lt;sub&gt;CPB&lt;/sub&gt;</td>
<td>1.57 (44)</td>
<td>NA</td>
</tr>
<tr>
<td>Vp (l/70 kg)</td>
<td>(BW/70)¹</td>
<td>32.8 (35)</td>
<td>NA</td>
</tr>
<tr>
<td>Residual variability, proportional</td>
<td>NA</td>
<td>0.23 (8)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Parameters were normalized to a 70-kg subject BW according to allometric scaling, to allow comparison with the same parameters in adults. * During CPB, Q is modified as follows: Q = 5.74 × (BW/70)⁰.⁷⁵ × (V<sub>CPB</sub>/500)¹.⁵⁷, where V<sub>CPB</sub> is the CPB prime volume in milliliters. BSV = between-subject variability (η); BW = body weight (kg); CPB = cardiopulmonary bypass; CL = elimination clearance; NA = not applicable; % RSE = percent relative standard error; Q = intercompartmental clearance; Vc = central volume of distribution; Vp = peripheral volume of distribution.

![Fig. 2. Diagnostic plots for the final population pharmacokinetic model. Observed tranexamic acid concentrations versus model-predicted concentrations (A) and the distribution for the corresponding normalized prediction distribution errors (NPDE) metrics (B). NPDE versus time (C) or predicted concentrations (D). The lines indicate the lines of unity (A and B) and the y = 0 line (C and D). NPDE statistics, mean, and variance were not significantly different from 0 (Wilcoxon signed rank test, P = 0.56) and 1 (Fisher’s variance test, P = 0.52), and the distribution was not significantly different from a normal distribution (Shapiro-Wilk test of normality, P = 0.32). TA = tranexamic acid.](image-url)
Discussion

We have described for the first time the pharmacokinetics of TA in children undergoing cardiac surgery, which was satisfactorily described by an open two-compartmental model with linear elimination. The allometric adjustment of volumes and clearances explained a significant part of the BSV. This allometric scaling used power exponents of ¾ and 1 for clearance and volume terms, respectively, which clearly indicates that the clearance is not linearly related to body weight. Therefore, the dosing adjustment to obtain a plateau concentration is not a simple dose amount per kilogram but is a function of BW at the power of ¾ (BW0.75). The allometric theory is supported by a wide body of studies and by mathematical fractal theory (for a detailed review, see Anderson and Holford28). CPB also had a significant effect on the Q, which was dependent on the CPB prime volume. This latest point came as no surprise, because the ratio of the CPB circuit volume to the patient’s blood volume, greater for children than for adults, is known to be responsible for an important hemodilution effect that is able to have repercussions on drug pharmacokinetics.

The pharmacokinetics of TA during cardiac surgery with CPB has been previously described in adults.16 In this previous study, the model parameters were the central volume and the rate constants of elimination and transfer. The CPB was influencing k10, and there was no effect of BW on the constant rates. These differences in model parameterization and covariate effects make any comparison difficult. We could observe in the present study that TA clearance is approximately three times lower in children than in adults, whereas there are nearly twofold and fourfold increases in the volumes of the central and peripheral compartments, respectively.16 These differences are likely to result from the covariate modeling: the clearance terms were linearly related to BW, which inflates the clearance estimates, whereas they should have been related to BW at the power ¾. Increased distribution volumes in children as compared with adults were previously reported for the highly hydrophilic drugs (e.g., TA) ε-aminocaproic acid, atracurium, and ketorolac and were attributed to the developmental differences of body fluid compartmental volumes.17,29,30 In addition, Dowd et al. found that CPB induced an increase in the volume of distribution of the central compartment and reduced the elimination rate constant in adults. In contrast to our patients who were kept in normothermia, the temperature of adult patients in the previous study was maintained at 33°C during CPB, which could explain the changes in the elimination rate constant.

The absence of pharmacokinetic/pharmacodynamic studies with TA is the main reason for the absence of consensus concerning the effective target concentration and the appropriate dosing scheme for children. One could admit that the minimum effective concentration would be 16 µg/ml, which is the in vitro concentration inhibiting both fibrinolysis and platelet activation,20,21 and some authors retained 20 µg/ml as a minimal target to reach and maintain in cardiac surgery patients.16 In the discontinuous group of the present

Fig. 3. Individual pharmacokinetic time courses of tranexamic acid from 12 representative patients (+, observations; red line, mean population prediction; green line, individual predictions). TA = tranexamic acid.
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study, 92% of the children had pre-CPB TA concentrations lower than this 20-µg/ml threshold (vs. 33% in the continuous group). It is important to notice that these low concentrations were observed when the CPB is initiated and the patient's blood enters the CPB circuit, which leads to increased fibrinolysis. It is obviously desirable to have circulating concentrations effective at this time, and this observation reinforces the precedents regarding the usefulness of maintaining stable concentrations in patients with the help of continuous infusions.

Our simulations of the previously described dosing schemes showed that those with the highest dosages enabled the maintenance of concentrations greater than 20 µg/ml throughout surgery for children of all BWs, whereas for those with the lowest dosages, a concentration greater than 20 µg/ml was only partially maintained during surgery. However, the common characteristics of all these dosing schemes is the large range of concentrations that is observed for a given patient along the surgical procedure (twofold to approximately fivefold variation), in addition to the huge concentrations (as high as 700 µg/ml) that may be obtained with some schemes. The involvement of such high concentrations in the appearance of concentration-dependent side effects cannot be ruled out, suggesting that lower doses also effective at achieving the desired TA concentrations should avoid the occurrence of adverse effects.

The second aim of our work was consequently to propose a dosing scheme that would enable rapidly obtaining...
and maintaining effective TA concentrations, with amplitudes between maximal and minimal concentrations as low as possible. Dowd et al. recommended in adults a dosing scheme with a bolus dose followed by another dose in the CPB prime volume and a continuous infusion. The administration scheme in children may be even simpler, because the dose in the CPB prime volume does not seem to be required, according to our proposal. We indeed showed that a bolus dose of 6.4 mg/kg in combination with a weight-adjusted infusion (between 2.0 and 3.1 mg·h⁻¹·kg⁻¹) could enable the maintenance of TA concentrations between 20 and approximately 30 µg/ml, meaning that concentrations would be kept in a narrow range along the procedure. Our recommendations are in agreement with those reported in adults for an equivalent target concentration. However, the effective target concentration remains to be determined, because concentrations of approximately 20 µg/ml may be effective to suppress at least in part the in vitro fibrinolytic activity and platelet activation, but experiments on tissular extracts revealed that a full inhibition of fibrinolysis required concentrations of approximately 100 µg/ml. In line with this, concentrations as high as 126 µg/ml have been recommended for high-risk adult patients during cardiac surgery. Thus, further study will be needed to validate the dosing regimen proposed from our pharmacokinetic model in children, and to determine at what age or weight the pharmacokinetic profile in children is deemed equivalent to the one in adult patients. Furthermore, given that hemofiltration and hypothermia are frequently used, their putative effects remain to be determined. We could suppose that hemofiltration would lower TA concentrations and influence the apparent CL during the process. Hypothermia is known to slow distribution of substances between compartments and reduce their CL in addition to altering hemodynamics, which in turn can also alter pharmacokinetics. We can summarize the main limitations of our study as (1) the model is relevant for surgical procedures in normothermia and without hemofiltration; (2) our dosing recommendations would be worth testing in a cohort of patients proving the model; (3) we did not study any children younger than 12 months or any neonate younger than 30 days, who may have a very different clearance and volume of distribution; and (4) the small number of samples taken after stopping the infusion may have an influence on the precision of the estimated half-life.

In conclusion, we described for the first time the pharmacokinetics of TA in children undergoing cardiac surgery with CPB. We proposed from this model a dosing schedule for obtaining a selected target concentration throughout the

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Table 5. Dosing Proposal and Associated Pharmacokinetic Parameters for Tranexamic Acid in Children Undergoing Cardiac Surgery with Cardiopulmonary Bypass for a 20-µg/ml Target Concentration

<table>
<thead>
<tr>
<th>BW, kg</th>
<th>Loading Dose</th>
<th>Infusion Rate</th>
<th>Terminal Half-Life, h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg</td>
<td>mg/kg</td>
<td>CL, l/h</td>
</tr>
<tr>
<td>5</td>
<td>32</td>
<td>6.4</td>
<td>15.5</td>
</tr>
<tr>
<td>10</td>
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<td>96</td>
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<td>6.4</td>
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<tr>
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<td>255</td>
<td>6.4</td>
<td>80.4</td>
</tr>
</tbody>
</table>

Dosing regimen to readily obtain a plateau concentration of 20 µg/ml as a function of BW. The loading dose, given as a short infusion of approximately 5 min, is followed by a continuous infusion to maintain the target concentration. Because the pharmacokinetic is linear, the dose and rate should be multiplied by 2 for doubling the target concentration.

BW = body weight; CL = elimination clearance; Q = intercompartmental clearance; Vc = central volume of distribution; Vp = peripheral volume of distribution.

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Fig. 5. Dosing simulation to readily obtain a 20-µg/ml tranexamic acid concentration plateau after a 5-min loading dose followed by a 4-h infusion in children with body weights between 5 and 40 kg. The dotted horizontal line represents the threshold target concentration of 20 µg/ml. TA = tranexamic acid.
procedure. This work could serve as a basis for future studies to evaluate precisely—and under controlled TA concentrations—the effectiveness of TA in these patients, and most importantly for the in vivo determination of the most effective and safe target concentration.

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