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Population pharmacokinetics of tranexamic acid in adults undergoing cardiac surgery with cardiopulmonary bypass

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Editor's key points

- Tranexamic (TA) pharmacokinetics (PK) was satisfactorily described by an open two-compartmental model with linear elimination with either low- or high-dose continuous infusion schemes in adult cardiac surgery patients during cardiopulmonary bypass (CPB).
- The allometric adjustment of volumes and clearances explained a significant part of the between-subject variability.
- Bodyweight but not CPB influenced PK.
- To maintain a TA target concentration around 150 μg ml^{-1} in these patients, a specific continuous infusion scheme is proposed using the derived PK model.

Background. Interest in antifibrinolytic tranexamic acid (TA) has grown since the widespread removal of aprotinin, but its dosing during cardiac surgery is still debated. The objectives of this study were to investigate the population pharmacokinetics (PK) of TA given with either low- or high-dose continuous infusion schemes in adult cardiac surgery patients during cardiopulmonary bypass (CPB).

Methods. Patients were randomized to receive either low-dose (10 mg kg^{-1} followed by an infusion of 1 mg kg^{-1} h^{-1} throughout the operation, and 1 mg kg^{-1} into the CPB) or high-dose (30 mg kg^{-1}, then 16 mg kg^{-1} h^{-1}, and 2 mg kg^{-1} into the CPB) TA. Serum TA concentrations were measured in 61 patients and the data were modelled using Monolix.

Results. TA concentrations were 28–55 μg ml^{-1} in the low-dose group and 114–209 μg ml^{-1} in the high-dose group throughout surgery. TA PK was best described by a two-compartment open model. The main covariate effect was bodyweight, whereas the CPB did not influence the PK. Assuming a bodyweight of 70 kg, the population estimates were 4.8 litre h^{-1} for clearance, 6.6 litre for the volume of the central compartment, 32.2 litre h^{-1} for the diffusional clearance, and the peripheral volume of distribution was 10.8 litre.

Conclusions. The PK of TA was satisfactorily described by an open two-compartmental model, which was used to propose a dosing scheme suitable for obtaining and maintaining the desired plasma concentration in a stable and narrow range in cardiac surgery patients.

Clinical trial registration. ClinicalTrials.gov, NCT00809393.

Keywords: cardiopulmonary bypass; cardiovascular surgical procedures; pharmacokinetics; tranexamic acid

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Tranexamic acid (TA) [4-(aminomethyl)cyclohexane-1-carboxylic acid] is widely prescribed for the management of bleeding disorders and to reduce postoperative blood loss in patients undergoing high bleeding risk surgery.[1] Its use has increased since the BART study showed a consistent negative mortality trend associated with aprotinin use in high-risk cardiac surgery.[2] TA reduces blood loss or transfusion after off-pump[3 4] or cardiopulmonary bypass (CPB) surgery,[5–9] but the optimum dosing schedule is still debated. Horrow and colleagues[10] showed a decrease in blood loss in patients receiving 10 mg kg^{-1} followed by an infusion of 1 mg kg^{-1} h^{-1}. In another trial, the scheme of 30 mg kg^{-1} as loading dose (LD) followed by a 16 mg kg^{-1} h^{-1} infusion with TA also added into the pump prime was found to be more effective than a lower dosage.[5] Since the *in vitro* TA concentration required to suppress fibrinolysis is 10 μg ml^{-1},[11] the knowledge of TA pharmacokinetics (PK) is essential to determine the best dosage regimen. Although Fiechtner and colleagues[12] reported concentrations in patients receiving low-dose TA during CPB (10 mg kg^{-1} then 1 mg kg^{-1} h^{-1}), there have been until now few reports on PK data for TA during CPB.[13–15] One study described TA PK in 30 patients who received either a single bolus (50 or 100 mg kg^{-1}) or an LD followed with a low-dosage continuous infusion (10 mg kg^{-1} then 1 mg kg^{-1} h^{-1}).[13]

In their conclusions, the authors highlighted the need to maintain effective concentrations throughout the operation, suggesting that the scheme using a continuous infusion was the most appropriate, and proposed to administer a 30 mg kg^{-1} LD followed with a 16 mg kg^{-1} h^{-1} infusion for high-risk patients in order to maintain concentrations higher than 126 μg ml^{-1}. However, this proposal was not confirmed by assays in patients. Moreover, the PK of drugs may be altered by changes in the surgical procedure or in the CPB equipment,[16] which may result in a between-centre variability. There is thus significant interest to confirm and further investigate the PK of TA in this population of patients, which was the aim of our study. Analysis was performed in a subset population of a clinical outcome study, which revealed a better outcome in the high-dose group.[17] We report here the TA PK and propose a refined dosing scheme for the maintenance of effective and stable concentrations in these patients.

Methods

Clinical protocol

After local ethics committee (Comité de Protection des Personnes Île-de-France VIII, Boulogne-Billancourt, France) approval and written informed consent had been obtained, 569 patients were enrolled in the main clinical trial among whom 61 participated in the present PK study. The main study was quadri-centre, prospective, randomized, double-blind, and identified in clinicaltrials.gov (NCT00809393). Inclusion criteria were cardiac surgical procedure requiring CPB, including coronary artery bypass grafting (CABG), valve replacement or repair, aortic surgery, and endocarditis. Patients were divided into two groups for transfusion risk: those receiving dual antiplatelet therapy and those admitted for repeat CABG, valve replacement or repair, combined CABG and valve surgery, multiple valve surgery, surgery of the aorta, intracardiac tumour ablation or surgery for endocarditis were considered at high risk for transfusion. Patients were randomly assigned into one of the treatment groups: the low-dose group received an LD of 10 mg kg^{-1} TA (Exacyl®, Sanofi-Aventis, Paris, France) i.v. over 15 min, followed by an infusion of 1 mg kg^{-1} h^{-1} throughout the operation, and 1 mg kg^{-1} into the CPB prime volume. The high-dose group received 30 mg kg^{-1} over 15 min, followed by an infusion of 16 mg kg^{-1} h^{-1} throughout the operation, and 2 mg kg^{-1} into the CPB prime. Either an opioid-based anaesthetic supplemented with volatile agents or total i.v. anaesthesia with propofol, remifentanil, and neuromuscular blocking agents was used. All patients received heparin to achieve an activated clotting time >480 s and underwent non-pulsatile CPB with a membrane oxygenator (Synthesis, Sorin, Modena, Italy). The CPB circuit was primed with 1500 ml of Ringer's lactate solution and 250 ml of 1.4% sodium bicarbonate. The CPB pump flow was adjusted to maintain a mean arterial pressure >60 mm Hg and corporal temperature was allowed to drift to 33°C during CPB. A blood salvage device was used in all patients and transfusion was performed when needed according to the following rules: packed red blood cells if haemoglobin <80 g $litre^{-1}$ (60 g $litre^{-1}$ during CPB), frozen plasma when prothrombin time was <50%, platelets concentrate when platelet count was $<70 \times 10^9$ $litre^{-1}$, fibrinogen when fibrinogen was <1 g $litre^{-1}$.

Sample acquisition

Arterial blood samples were obtained in 61 consecutive patients from the principal investigator centre at the following times: pre-dose, 5 min after the LD, 10 min after the beginning of CPB, at discontinuation, and 1 h after discontinuation of the infusion. Serum was separated by centrifugation and stored at −80°C until analysis.

Drug assay

TA concentrations were determined using LC-MS/MS according to a fully validated procedure.[18] The method was linear in the range 1.0 (limit of quantification) to 200 μg ml^{-1}. Intra- and interday coefficients of variation were lower than 8.1% and 9.7% respectively, with intra- and interday accuracies ranging from 93.2% to 100.5%.

PK modelling

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

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

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

where A_1 and A_2 are the amounts of drug in the compartments; k_{10}=CL/V_c, k_{12}=Q/V_c, and k_{21}=Q/V_p, where Q is the intercompartmental clearance, V_c the volume of the central compartment, and V_p the volume of the peripheral compartment.

To test the effect of CPB, a parameter relating the CPB to a modification of any of the PK parameters (P) was included in the model as follows:

$$P = P_{TYPICAL} \times (1 + \theta_{CPB})$$

and this parameter was applied from the start to the end of the CPB procedure.

Data analysis

Data were analysed using the non-linear mixed-effect modelling software program Monolix version 4.1.2.[19] 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 (ϵ_{PROP}), and the between-subject variability (BSV or η) was ascribed to an exponential error model. Parameter shrinkage was calculated as $[1 - SD(\eta)/\omega]$, where $SD(\eta)$ and ω are the standard deviation of individual η parameters and the population model estimate of the BSV, respectively. The likelihood ratio test including the log-likelihood, the Akaike information criterion,

and the Bayesian information criterion (BIC) was used to test different hypotheses regarding the final model, covariate effect on PK parameters, residual variability model (proportional *vs* proportional plus additive error model), structure of the variance–covariance matrix for the BSV parameters. Diagnostic graphics and other statistics were obtained using the R program.[20] From the final model, 500 simulations were performed to compute the visual predictive check (VPC) and the normalized prediction distribution error (NPDE) metrics, whose mean, variance, and distribution must not be different from 0, 1, and a normal distribution.[21] Because the doses and infusion times were different between individuals, prediction-corrected VPCs (pcVPC) that normalize the observed and simulated dependent variable by the typical population prediction ('Uppsala' correction) were computed and represented.[22] The median prediction error (MDPE) and median absolute prediction error (MDAPE) were also calculated both for the individual and for the population PK parameters, with MDPE=median [(measured TA concentration−predicted TA concentration)/predicted TA concentration].

Results

Population characteristics and TA concentrations

The characteristics of the patients are presented in Table 1. There were no differences between the two dose groups. The mean TA concentrations are shown in Supplementary Figure S1 (Supplementary Appendix). In the low-dose group, concentrations during surgery were in the range 15.4–82.5 μg ml^{-1}. For two patients of this group, the concentration was below 16 μg ml^{-1} at the end of the infusion. In the high-dose group, TA concentrations were always >114 μg ml^{-1} during the infusion. However, 10 values (=11% of the total number of values) were lower than 126 μg ml^{-1} during surgery and maximal concentrations reached up to 209 μg ml^{-1}. There were two temporal profiles for concentration curves: in the low-dose group, the maximal concentration was observed 5 min after the LD and decreased in a time-dependent manner until the last time point despite the maintenance infusion. In the high-dose group, the concentration achieved after the LD kept increasing until the end of the continuous infusion (Supplementary Fig. S1).

Population PK modelling

PK time-courses were best described by a two-compartment open model. The model parameters were defined as the elimination and diffusional clearances, CL and *Q*, and the volume of the central and peripheral compartments, V_c and V_p. BSVs could be estimated for CL, V_c and *Q* only. Residual variability was described by a proportional error model. At this step, CL was 4.9 litre h^{-1} [relative standard errors (RSE 6%)] and the corresponding BSV was 0.41 (RSE 10%).

The main covariate was body size. Table 2 summarizes the model building steps for the body size effects. The PK parameters were allometrically normalized for bodyweight to a 70 kg individual as follows:

$$P_i = P_{TYPICAL} \times \left(\frac{BW_i}{70}\right)^{PWR}$$

Table 1 Subject characteristics and operative data for low- and high-dose patients. Normally distributed data (as evaluated with the D'Agostino–Pearson normality test) are presented as the mean (SD), whereas not normally distributed data are given as the median (25th–75th percentiles). CABG, coronary artery bypass graft; AVR, aortic valve replacement; CPB, cardiopulmonary bypass

	Low dose	High dose
n	30	31
Female/male	9/21	7/24
Age range (yr)	41–81	47–83
Bodyweight (kg)	74.5 (60.0–86.3)	75.0 (70.0–86.0)
Height (cm)	171 (156–173)	171 (168–175)
Bleeding risk group		
Low risk	15	16
High risk	15	15
Type of surgery		
CABG	20	22
Mitral valvuloplasty	3	0
Mitral valve replacement	1	0
AVR	2	4
Aortic surgery	3	4
Intracardiac tumour	1	0
CABG+AVR	0	1
CPB duration (min)	87.3 (48.4)	93.2 (48.4)
Surgery duration (min)	255.0 (50.8)	261.0 (42.7)
Preoperative serum creatinine (μM)	91.5 (74.8–115.3)	88.0 (78.0–98.0)

Table 2 PK model building. η, between-subject variability; AIC, Akaike information criterion; BIC, Bayesian information criterion; TV, typical value of parameter; BW, bodyweight in kg; $\Sigma\eta^2(CL,V_c,Q)$ denotes the sum of between-subject variances (η^2s) 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

Model	Details	AIC	BIC
A. Two compartment	CL, V_c, Q, V_p $\Sigma\eta^2(CL,V_c,Q)=0.399$	2015	2032
B. (A)+effect of bodyweight*	CL or $Q=TV\times(BW/70)^{0.75}$ V_c or $V_p=TV\times(BW/70)^{1}$ $\Sigma\eta^2(CL,V_c,Q)=0.276$	1940	1957
C. (B)+effect of CPB	CL, V_c, Q, V_p $P=TV(P)\times(BW/70)^{PWR}\times(1+\theta_{CPB})$		
On V_c	$\Sigma\eta^2(CL,V_c,Q)=0.352$	1986	2007
On CL	$\Sigma\eta^2(CL,V_c,Q)=0.345$	2033	2054
On Q	$\Sigma\eta^2(CL,V_c,Q)=0.224$	2008	2029
On V_p	$\Sigma\eta^2(CL,V_c,Q)=0.265$	2001	2022

Table 3 Parameter estimates of the final TA population model in 61 patients. Parameters are normalized after a 70 kg subject bodyweight (BW) according to allometric scaling. % RSE, per cent relative standard error; BSV, between-subject variability (η); CL and Q, elimination and intercompartmental clearances; V_c and V_p, central and peripheral volumes of distribution; NA, not applicable

Parameter	Covariate effect	Estimate (% RSE)	BSV (% RSE) (shrinkage)
CL (litre h^{-1} 70 kg^{-1})	$(BW/70)^{0.75}$	4.8 (5)	0.34 (10) (0.04)
V_c (litre 70 kg^{-1})	$(BW/70)^{1}$	6.6 (20)	0.28 (25) (0.31)
Q (litre h^{-1} 70 kg^{-1})	$(BW/70)^{0.75}$	32.2 (15)	0.29 (32) (0.48)
V_p (litre 70 kg^{-1})	$(BW/70)^{1}$	10.8 (14)	NA
Residual var., prop.	NA	0.11 (7)	NA

where *i* denotes the *i*th individual. The PWR exponents were set to $\frac{3}{4}$ and 1 for the clearance and volume terms, respectively. This decreased significantly the BSV estimate (BSV of CL decreased from 0.41 to 0.34) and improved the predictive performance of the model with a decrease of 75 units in BIC. We tested the influence of CPB on TA PK, but we did not detect any significant effect on the PK parameters, as shown in Table 2. Supplementary Figure S2 (Supplementary Appendix) depicts the improvement of the predictive performance of the final model. No influence of age, sex, and bleeding risk group on the PK could be found for the analysed subjects. Table 3 shows the final population PK estimates. Most of the parameters were well estimated with low RSE. The empirical Bayesian estimate shrinkages were low. The goodness-of-fit plots are depicted in Figure 1A and B. The prediction-corrected VPC shows that the median of observed data is well included within the 95% confidence interval (CI) of the simulated data (Fig. 1C and D). MDPE for the population and individual PK parameters were −5% and 1% respectively, while the corresponding values of MDAPE were 15% and 5%. The model predictions were also investigated by plotting the observed-to-individual predicted concentrations *vs* time. The variations did not roughly exceed ±20% (Supplementary Fig. S3, Supplementary Appendix) and the error remained constant over time, demonstrating good performances from early to late time points. Figure 2 shows representative PK time-courses for some low- and high-dose patients. Our simulations in high-dose patients clearly indicate that concentrations >200 μg ml^{-1} may be reached immediately after the LD or at the end of the continuous infusion, whereas the awaited maximal concentrations with this recommended dosing scheme were about 150 μg ml^{-1}.[13]

Dosing proposal

There was evidence from our outcome-oriented study[17] that high-dose TA was more effective than the lower dose on several endpoints. The objective of this dosing scheme was to obtain and maintain a plateau concentration of 126 μg ml^{-1} throughout surgery.[13] However, the mean TA concentrations in this group were 147–167 μg ml^{-1} during this period, with for some patients minimal concentrations lower than 126 μg ml^{-1} and maximal concentrations at the end of infusion >200 μg ml^{-1}. Furthermore, as shown in Supplementary Figures S1 (Supplementary Appendix) and S2, concentrations keep increasing in time during the continuous infusion (up to 40% increase between the start and the end of CPB). This may be a concern in the case of long-lasting surgery, where concentrations even higher than 200 μg ml^{-1} may thus be reached. Moreover, this dosage regimen exposes patients to total doses as high as 96 mg kg^{-1} for a 4 h surgery, which is near the doses of 126 mg kg^{-1} per day associated with retinal changes in the cat and rabbit studies after several days, according to the package insert. For all these reasons, we hypothesized that keeping concentration in a narrower range centred on the effective plateau target would be the most appropriate, and proposed a refined dosing scheme to this end. The critical moment for TA action is when the patients' blood entered into contact with the CPB circuit, which is known to activate fibrinolysis. In patient's samples obtained just after the CPB initiation, the mean concentration was 152 μg ml^{-1} in

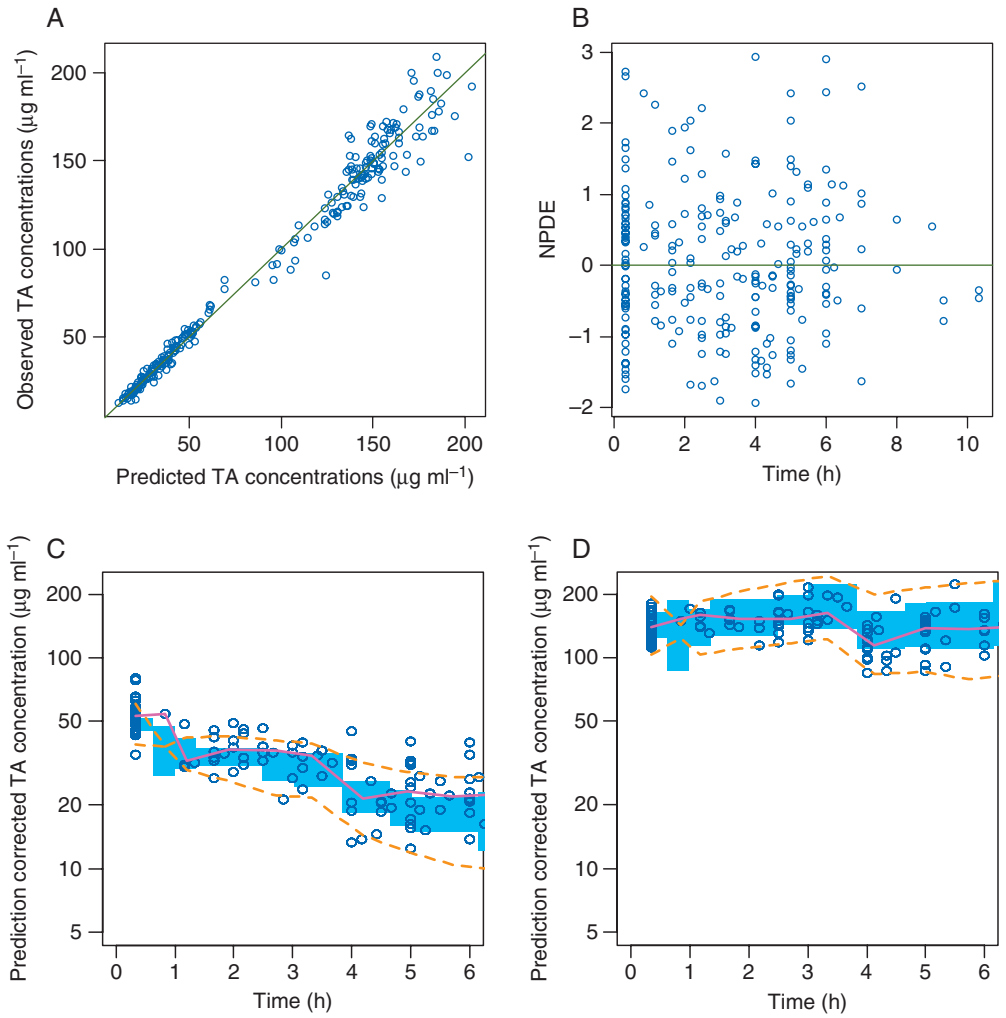

Fig 1 Diagnostic plots for the final population PK model. (A) Observed TA concentrations *vs* individual predicted concentrations; (B) NPDE *vs* time. The lines indicate the lines of unity (A) and the $y=0$ line (B). NPDE statistics, mean, and variance were not significantly different from zero (Wilcoxon's signed-rank test, $P=0.86$) and 1 (Fisher's variance test, $P=0.77$). VPC in the low-dose (C) and high-dose (D) groups. The VPC should be considered as an approximation because VPC suppose that the dose and infusion times are similar. The doses differences, but not the infusion time differences, are appropriately taken into account thanks to the 'Uppsala' correction. The solid centre lines and the shaded areas stand for the median of observations and the 95% CI of the predictions in the time intervals. The dashed lines stand for the 10th and 90th percentiles of the predictions.

the high-dose group, which led us to retain 150 µg ml^{-1} as the target concentration. As bodyweight was the main parameter affecting the PK, we propose a dosing regimen adjusted for patients between 50 and 75, 75 and 100, and 100 and 125 kg. We found that an infusion of 46 mg kg^{-1} given in 1 h followed with an 11 mg kg^{-1} h^{-1} continuous infusion throughout surgery (without dosing in the CPB prime volume) should allow us to maintain the target concentration in patients weighing between 50 and 75 kg. After the same 46 mg kg^{-1} in 1 h infusion, the rate of the second infusion should be decreased to 10 mg kg^{-1} h^{-1} for patients between 75 and 100 kg, and to 9 mg kg^{-1} h^{-1} for those between 100 and 125 kg. As illustrated in Figure 3, our proposal allows us to maintain stable blood concentrations between 150 and about 190 µg ml^{-1} at all time points and in all patients. The dosing proposal and associated PK parameters in individuals between 50 and 125 kg are presented in Table 4.

Discussion

Our study is one of the largest investigations ($n=61$) examining the PK of an antifibrinolytic during CPB. In a previous work, Dowd and colleagues[13] hypothesized that a certain TA concentration must be exceeded at all times for consistent efficacy, justifying the use of a continuous infusion, and recommended a dosing scheme for maintaining a plateau 126 µg ml^{-1} concentration during surgery. We demonstrated that this dosage regimen resulted, as expected, in the mean concentrations greater than this 126 µg ml^{-1} threshold, but with extreme values at 114 and 209 µg ml^{-1} and with a constant increase

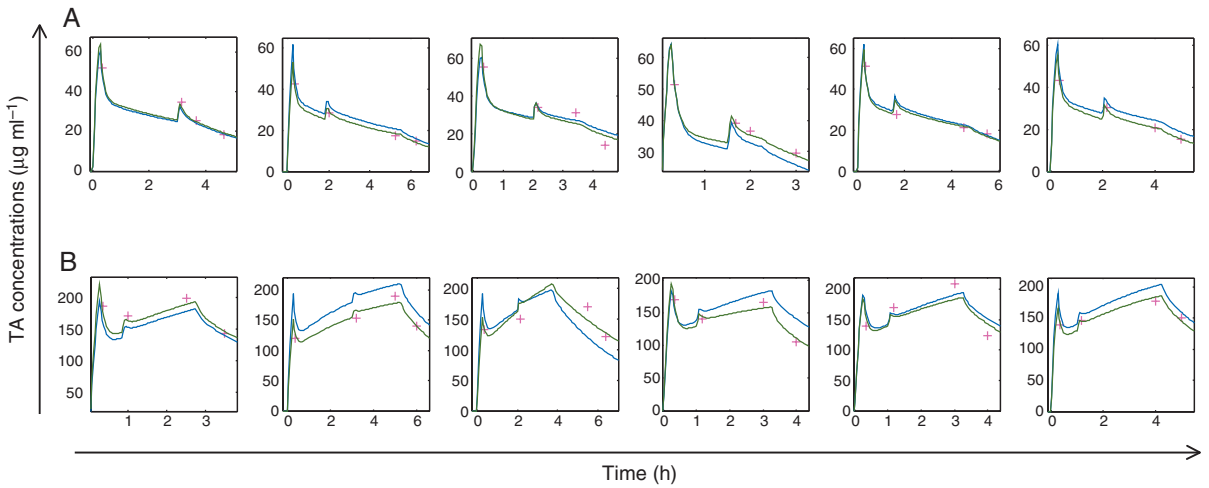

Fig 2 Individual PK time-courses of TA in examples of low-dose (A) and high-dose (B) patients: (+, observations; blue line, mean population prediction; green line, individual predictions).

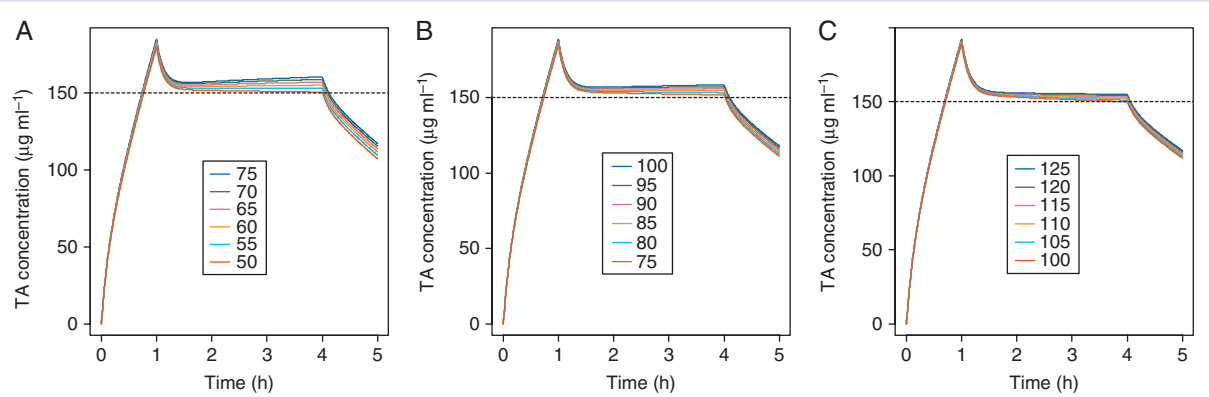

Fig 3 Dosing simulation in order to obtain a 150 μg ml^{-1} TA concentration plateau after a 46 mg kg^{-1} infusion in 1 h followed by an 11 mg kg^{-1} h^{-1} infusion in patients with bodyweights between 50 and 75 kg (A), after a 46 mg kg^{-1} infusion in 1 h followed by a 10 mg kg^{-1} h^{-1} infusion in patients with bodyweights between 75 and 100 kg (B), or after a 46 mg kg^{-1} infusion in 1 h followed by a 9 mg kg^{-1} h^{-1} infusion in patients with bodyweights between 100 and 125 kg (C). Infusion time for the second infusion was set at 3 h. The dashed horizontal lines represent the threshold target concentration of 150 μg ml^{-1}.

in time during the continuous infusion. In the low-dose group, TA concentrations were in agreement with those observed with the same scheme.[12] It is noteworthy that concentrations in all low-dose group patients were >17 μg ml^{-1} during surgery (except two values at 14.3 and 15.4 μg ml^{-1}). Knowing that TA concentrations required to suppress fibrinolysis and plasmin-induced platelet activation are 10 and 16 μg ml^{-1}, respectively,[11 23] our results together with those of the efficacy study (showing a better outcome for high-dose patients)[17] clearly demonstrate that achieving only these thresholds is insufficient to fully explain the PK/PD relationship of TA. This point will be further discussed thereafter.

Our modelling then showed that TA PK 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 $\frac{3}{4}$ and 1 for clearance and volume terms, respectively. The allometric theory is supported by a wide body of studies and mathematical fractal theory.[24] In contrast to the study by Dowd and colleagues[13] who reported that CPB may affect TA PK (the CPB induced an increase of 15% for the volume of the central compartment and a decrease of about 39% of the elimination clearance for a 70 kg individual), we did not observe any significant effect of CPB. However, as

Table 4 Dosing proposal and associated PK parameters for TA in adults between 50 and 125 kg undergoing cardiac surgery with CPB for a 150 μg ml^{-1} target concentration. The first infusion, given in ~1 h, is followed by a continuous infusion throughout surgery to maintain the target concentration. CL and *Q*, elimination and intercompartmental clearances; V_c and V_p, central and peripheral volumes of distribution

Bodyweight (kg)	Infusion 1 (1 h)		Infusion 2		CL (litre h^{-1})	*Q* (litre h^{-1})	V_c (litre)	V_p (litre)	Terminal half-life (h)
	mg	mg kg^{-1}	mg h^{-1}	mg h^{-1} kg^{-1}					
50	2300	46	1650	11	3.7	4.7	25.0	7.7	2.5
55	2530	46	1815	11	4.0	5.2	26.9	8.5	2.5
60	2760	46	1980	11	4.2	5.7	28.7	9.3	2.6
65	2990	46	2145	11	4.5	6.1	30.5	10.0	2.6
70	3220	46	2310	11	4.8	6.6	32.2	10.8	2.7
75	3450	46	2475	11	5.0	7.1	33.9	11.6	2.7
80	3680	46	2400	10	5.3	7.5	35.6	12.3	2.8
85	3910	46	2550	10	5.5	8.0	37.2	13.1	2.8
90	4140	46	2700	10	5.7	8.5	38.9	13.9	2.9
95	4370	46	2850	10	6.0	8.9	40.5	14.7	2.9
100	4600	46	3000	10	6.2	9.4	42.1	15.4	2.9
105	4830	46	2835	9	6.4	9.9	43.6	16.2	3.0
110	5060	46	2970	9	6.7	10.3	45.2	17.0	3.0
115	5290	46	3105	9	6.9	10.8	46.7	17.7	3.0
120	5520	46	3240	9	7.1	11.3	48.2	18.5	3.1
125	5750	46	3375	9	7.3	11.8	49.7	19.3	3.1

there was a bolus dose in the prime volume, the dilution if any would be negligible, that is, it was not expected to observe a simultaneous and rapid decrease in TA concentration. The sparse sampling after the start of the CPB may also be an explanation (and may as well be the reason why the BSV of V_p could not be estimated). Furthermore, this difference may at least in part be related to variations in the patient population, the surgical procedure, the CPB materials, and the model parameterization.[16] In the study by Dowd and colleagues,[13] the model parameters were indeed the central volume and the rate constants of elimination and transfer; there was no effect of bodyweight on the constant rates; and clearance terms were linearly related to bodyweight. These differences in model parameterization and allometric scaling may also impact the variability of the model predictions, which was truly acceptable in the present work since the predicted concentrations were roughly equal to ± 20% the observed concentrations in both dose groups and for all time points. In accordance with our findings, a recent study in five patients where all the PK parameters except the elimination rate constant were fixed according to Dowd's model revealed similar TA clearance before, during, and after CPB.[15] The absence of significant effect of CPB on the PK of drugs given during cardiac surgery has also previously been reported,[25 26] and is in agreement with a CPB technique most respectful of physiological processes.

Even if the clinical data in our study are in agreement with satisfying efficacy and safety of the high-dose TA dosing scheme,[17] the following points need to be considered: (i) 11% of TA concentration values with this scheme were lower than 126 μg ml^{-1} during surgery, which may be a concern since this threshold was proposed as the effective concentration to maintain; (ii) maximal concentrations as high as about 210 μg ml^{-1} were reached; and (iii) TA concentrations during surgery were not a stable plateau but kept increasing with time, exposing patients to the risk of reaching even higher plasma concentrations in the case of long-lasting surgery and to the potential-associated concentration-dependent side-effects. Less variability and better outcomes for both efficacy and safety may thus be expected if this PK profile was improved, which was the basis for our new dosage regimen proposal. This scheme is quite simple since it consists of a first 1 h 46 mg kg^{-1} continuous infusion to reach the target concentration, after which a single change in the flow rate to 9, 10, or 11 mg kg^{-1} h^{-1} (depending on the patient's bodyweight) enables the desired concentration to be maintained. For a 4 h surgery, the total dose is then between 73 and 79 mg kg^{-1}, which is 18–24% less than with the previously recommended dosage regimen, reducing the risks of adverse events, whereas the same effective concentration is maintained during surgery, but in a much more stable manner.

We adopted 150 μg ml^{-1} as the target plateau to maintain because it was the mean measured concentrations at the beginning of CPB, but we recognize that our study design did not enable to precisely determine the effective concentration. We assumed that this target could be appropriate, considering that: (i) concentrations as high as 100 μg ml^{-1} may be required for achieving a 98% fibrinolysis inhibition in tissue extracts, (ii) TA was described to inhibit fibrinolysis and platelet activation for concentrations below 20 μg ml^{-1}, but another potential mechanism of action might be the increase in thrombin formation, which requires concentrations as high as 126–252 μg ml^{-1} to be therapeutic,[27 28] and (iii) the maintenance of such a concentration in our

high-dose group did not reveal particular safety concerns.[17] However, these data suggest that the mechanism of action of TA remains to be explored more in depth and might be more complex than only inhibition of fibrinolysis, which is already inhibited by about 90% for TA concentrations around 20 $\mu g\ ml^{-1}$.[11]

The main limitations of our study are the small number of samples obtained after stopping the infusion which may influence the precision of the estimated half-life, together with the need for further study to validate our dosing proposal with TA assays in patients receiving the recommended dosage. Since there were no patients with renal impairment in our population, our study thus cannot be extrapolated to such patients.

In summary, our study was the first designed to assess TA PK in cardiac surgery patients with CPB with two different continuous infusion regimens. We described herein an appropriate model for the prediction of TA PK, showing an effect of bodyweight but not CPB. Altogether, the results of our pharmacodynamic[17] and PK studies (present work) provide compelling evidence for the rationale use of a TA target concentration around 150 $\mu g\ ml^{-1}$ in these patients. This concentration could be maintained by the use of a 1 h 46 mg kg^{-1} infusion, followed by a weight-adjusted 9, 10, or 11 mg $kg^{-1}\ h^{-1}$ infusion throughout the surgery.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Authors' contributions

S.G.D. and S.U. designed the study, collected and analysed the data, and drafted the paper. B.T. and M.F. designed the study and recruited patients. E.A., J.C.A., and P.D. critically revised the data and the manuscript. S.G.D., B.T., E.A., M.F., J.C.A., P.D. and S.U. approved the final version of the manuscript.

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Declaration of interest

None declared.

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