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Title: Pharmacokinetic modeling of tranexamic acid for patients undergoing cardiac surgery with normal renal function and model simulations for patients with renal impairment

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Attestation

QY, AJ, RRB, MW, and KSP reviewed the data and attested to approval of the final manuscript. All authors attest to the integrity of the data and analyses reported. MW is the archival author.

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GLOSSARY

BART	Blood Conservation Using Anti-fibrinolytics in a Randomized Trial
BSV	between-subject variability
BW	body weight
CL_R	renal clearance
CL_{12} or CL_{21}	inter-compartmental clearances from central to peripheral compartments and from peripheral to central compartments, respectively
CL_{Cr}	creatinine clearance
CRD	chronic renal dysfunction
CV	coefficient of variation
GFR	glomerular filtration rate
KDOQI	Kidney Disease Outcome Quality Initiative
MD	maintenance infusion dose
OFV	objective function value
PK	pharmacokinetics
Q_3	flow rate between central and extracorporeal compartments (the CPB pump circuit)
Scr	serum creatinine concentration
TXA	tranexamic acid
V_1, V_2 and V_3	volumes of distribution of the central, peripheral and extracorporeal compartments, respectively

ABSTRACT

Tranexamic acid (TXA), an effective antifibrinolytic agent that is cleared by glomerular filtration, is widely used for cardiopulmonary bypass (CPB) surgery. However, an effective dosing regimen has not been fully developed in patients with renal impairment. The aims of this study are to characterize the inter-patient variability associated with pharmacokinetic parameters and to recommend a new dosing adjustment, based on the BART dosing regimen for CPB patients with chronic renal dysfunction (CRD). Recently published data on CPB patients with normal renal function (n=15) were re-examined with a two-compartment model using the ADAPT5® and NONMEMVII® to identify covariates that explain inter-patient variability and ascertain whether sampling strategies might affect parameter estimation. A series of simulations was performed to adjust the BART dosing regimen for CPB patients with renal impairment. Based on the 2-compartmental model, the number of samples obtained after discontinuation of TXA infusion was found not to be critical in parameter estimation ($P > .05$). Both body weight and creatinine clearance were identified as significant covariates ($P < .005$). Simulations showed significantly higher than normal TXA concentrations in CRD patients who received the standard dosing regimen in the BART trial. Adjustment of the maintenance infusion rate based on the percent reduction in renal clearance resulted in predicted plasma TXA concentrations that were safe and therapeutic (~ 100 $mg \cdot L^{-1}$). Our proposed dosing regimen, with consideration of renal function, is able to maintain effective target plasma concentrations below those associated with toxicity for patients with renal failure for CPB.

***Key word*: Tranexamic acid, cardiopulmonary bypass, pharmacokinetic or population modeling, dose optimization**

INTRODUCTION

Tranexamic acid (TXA) is an anti-fibrinolytic agent used widely to minimize blood loss and transfusion during cardiac surgery with use of cardiopulmonary bypass (CPB). This synthetic lysine derivative has class I recommendation as a blood conservation strategy for cardiac surgical patients [1]. Previous studies have reported that 100 $mg \cdot L^{-1}$ TXA in plasma is sufficient to allow for a complete anti-fibrinolytic effect [2], and the value was adopted as the desired therapeutic concentration for high-risk cardiac surgery patients. The dosing strategy developed by Dowd and coworkers [3] (loading infusion of 120 $mg \cdot kg^{-1} \cdot h^{-1}$ for 15 min, followed by 16 $mg \cdot kg^{-1} \cdot h^{-1}$ for 10 h) for TXA for cardiac surgery with use of cardiopulmonary bypass among patients with normal renal function (see Appendix A) was adopted by the BART Trial (Blood Conservation Using Anti-fibrinolytics in a Randomized Trial) [4]. As a result, this strategy has become widely used despite the fact that the optimal dosing regimen for TXA continues to be debated. This is particular true in regards to the reduction of the maintenance infusion duration [5].

The characteristic of cardiac surgical population is changing; there are more older patients with a greater burden of comorbid diseases, and typically patients undergo increasingly more complex and high-risk surgery with high blood transfusion requirements. More specifically, approximately 50% of our surgical population has chronic renal dysfunction (CRD) and incurs a high risk of postoperative morbidity and mortality [6]. This is of particular concern with respect to TXA, a drug that is primarily eliminated via glomerular filtration [7, 8]. There are considerable safety and cost implications for high TXA (60-260 $mg \cdot kg^{-1}$) doses that may render patients susceptible to postoperative non-ischemic seizures, prolonging ICU and hospital stay [9-13]. Given this high risk patient population, there is no consensus on the optimal dosing regimen.

Our study has two specific aims. First, we revisited some recently published data [5, 14] on cardiac surgical patients with normal renal function who were given the BART dose to identify important patient-specific covariates that may affect TXA disposition using a population pharmacokinetic modeling approach. Secondly, we utilized the model developed to explore an optimal dosing algorithm using a series of simulations of patients with various severity of CRD to determine if the proposed regimen can maintain stable TXA concentrations at the therapeutic target concentration (100 $mg \cdot L^{-1}$).

METHODS

Information on Patient Data for TXA Administration

Published works of Wąsowicz [14] and Sharma [5] and coworkers consisted of concentration-time data on TXA for fifteen patients with normal renal function undergoing cardiac surgery with use of CPB. Patient demographics and peri-operative variables are summarized in Supplemental Table 1. Within these studies, TXA was administered using a modified BART dosing regimen consisting of a 120 $mg \cdot kg^{-1} \cdot h^{-1}$ (30 $mg \cdot kg^{-1}$) loading dose infused over 15 min followed by 16 $mg \cdot kg^{-1} \cdot h^{-1}$ maintenance infusion until chest closure (~3.5 h), with an additional 2 $mg \cdot kg^{-1}$ bolus dose given within the CPB pump prime (~2 L). The CPB flow was approximately 5 $L \cdot min^{-1}$. Pharmacokinetic (PK) analysis was performed after dividing the cardiac operation duration into 5 phases: for the loading infusion dose (Phase I), chest open (Phase II), CPB (Phase III), chest closure (Phase IV) and washout (Phase V); the maintenance infusion was given over Phases II to IV (see appendix A). Sampling was conducted over the five phases, with continued sampling during the washout period or Phase V after cessation of infusion. Similar schedules were found for both studies, with the exception that more samples were taken during Phase V for the Sharma study [5] (6-8 samples) compared to Wąsowicz study (2 samples) [14]. Additionally, the maintenance infusion used by both studies was substantially shorter at 3.5 h compared to BART regimen at 10 h [3].

Modeling and Simulations

Compartment model fitting to data. With the assumption that fluids in extracorporeal device (2L in volume) was not returned to patients at the end of surgery, a two compartment model was used to fit data for all phases simultaneously using ADAPT® (BMSR version 5, USC, Los Angeles, CA; see Appendix B for model and equations) to examine whether the number of samples obtained after discontinuation of TXA infusion is important for parameter

estimation. TXA was assumed to be 100% eliminated by kidney. The computational algorithm used was the maximum likelihood solution via the EM algorithm (MLEM), and the error variance function was defined as $VAR_i = (\sigma_1+\sigma_2 \cdot Y(\theta,t_i))^2$, where σ_1 is SD_{inter} and σ_2 is SD_{slope}. Differences in the estimates were compared using the Mann Whitney U test.

Population modeling and covariates. Data from all 15 patients described by Sharma [5] and Wąsowicz and colleagues [14] were used for population analysis to identify important covariates that confer between- or inter-subject variability (BSV) and to estimate population parameters with NONMEMVII® (ICON Development Solution, version 7.2, Ellicott City, MD). The algorithm used to arrive at the best model was via stochastic approximation EM (SAEM). Initially, a base population model was constructed without any covariates added (equations in Appendix B). As body weight and creatinine clearance are continuous variables, their effect on clearance (CL) or volume of distribution (V_1) can be expressed in forms of linear, power and exponential functions in relation to their medians [15]. Improvement of fit was compared after adding each covariate combination to specific pharmacokinetic parameters and appraised with the use of objective function values (OFVs), which approximates -2 times the log-likelihood. The difference in -2 log likelihood across nested models approximates a Chi-square distribution. A stringent α-level (0.005) for significance was used to judge improvement to the model. The model with the greatest improvement of fit was selected to be the final model. The internal validation techniques including basic goodness plots and visual predictive check plots were used to examine whether the final covariate model can adequately describe the data without bias.

Simulations. We conducted simulations using the 2-compartmental model to appraise the recent protocol of returning fluids in extracorporeal device to central compartment at end of CPB (Appendix B). We then simulated the impact of renal impairment upon plasma TXA concentrations when the BART dosing regimen was administered, or when 50 $mg \cdot kg^{-1}$ of

TXA was infused over 15 min (200 $mg \cdot kg^{-1} \cdot h^{-1}$) among patients of varying severity of renal dysfunction. This was achieved by setting the CL_R (which equals GFR) as 100, 75, 50, 25, 10 and 1% CL_R (see supplemental Table 2) to denote varying degrees of renal insufficiency. According to the Kidney Disease Outcome Quality Initiative (KDOQI) clinical practice guideline [16, 17], the severity of chronic kidney disease can be categorized according to GFR ($mL \cdot min^{-1} \cdot 1.73m^{-2}$) (Supplemental Table 2). These simulation parameters were utilized to subsequently develop a dosing strategy for patients with renal failure.

RESULTS

Fitting. Our compartmental model fitted both sets of TXA data well, regardless of the number of samples [fewer [14] (Fig. 1A) or more [5] (Fig. 1B)] obtained after the infusion was stopped. The model demonstrated an accumulation of TXA in plasma during the first 5 min (~ 170 $mg \cdot L^{-1}$), which remained at approximately 150 $mg \cdot L^{-1}$ during the chest opening and CPB periods (Phases II and III). The model further showed that, upon termination of the maintenance infusion, TXA concentrations gradually decreased in a first-order manner over time (Fig. 1). Here, we found that the estimated parameters for renal clearance (CL_R), central volume of distribution (V_1), inter-compartmental clearances [$CL_{12} = k_{12}V_1$ (or $CL_{21} = k_{21}V_2$)] and peripheral volume of distribution (V_2) were not significantly different between the two groups ($P > .05$; Table 1). However, parameters derived from the fit to the richer data set (Sharma and coworkers [5]) were associated with a smaller coefficient of variation (CVs) as the larger number of data points would reduce the uncertainty in parameters estimates (Fig. 1; Table 1). We further performed simulations and found that the return of circuit fluids from the extracorporeal circuit after CPB did not perturb TXA kinetics (data not shown).

Population and covariate model. Model testing, with incremental addition of covariates to the base model, led to the final model (I) that contained body weight and CL_{Cr} as covariates, and showed significantly reduced inter-patient variability in CL_R (Δ=22.3%), V_1 (Δ=19.9%), CL_{12} or CL_{21} (Δ=86.4%) and V_2 (Δ=1.7%) (see Table 2 for detailed covariate model building steps). The CPB duration (τ_{CPB}) or infusion (τ_{TXA}) time were found not to be important (data no shown). Improvement of model fit in model I, with incorporation of covariate effects of body weight and CL_{cr} on V_1 and CL_R, was seen when the regression line and the line of identity coalesce, and observations were similar to predictions (Fig. 2A). The population parameters estimated from final covariate model (model I) are summarized in Table 2. The

objective function value (OFV) revealed goodness of model fit, decreasing by 74 units (from 591 to 517) with 3 degrees of freedom and reflecting a significant improvement based on the likelihood ratio test that corresponds to $P < .005$ (Table 2). Conditional weighted residuals were evenly distributed around zero and followed normal distribution, indicating reasonably reliable parameter estimation (Figs. 2B-D). The visual predictive check plot (replicate=100) showed the median and 95^{th} and 5^{th} percentiles of observed data lay within simulated concentration sampling distribution with 90% confidence interval (Fig. 2E). The %shrinkage, an index suggestive of reliability of fit and covariate identification, for CL_R, V_1, CL_{12} or CL_{21} and V_2 were 1.01%, 2.39%, 4.22% and 4.01% respectively, and the shrinkage for residual variability is 4.01%. Since these values are close to zero, individual prediction and individual estimates should be reliable (Table 2).

Simulations

Dose adjustment of maintenance or loading infusion rate in CRD patients undergoing CPB. The procedure of return of pump fluids has been currently instituted in the surgical protocol at our institution for CPB. Simulations were based upon the BART regimen with return of the pump contents (TXA + fluids) at the end of bypass in patients with varying severity of renal dysfunction. We found that the simulated, initial plasma TXA concentrations at 5 min were comparable for all levels of renal impairment, but plasma TXA continued to rise to potentially toxic concentrations with increasing severity of renal dysfunction (Fig. 3A). We then adjusted the maintenance infusion rate in proportion to the reduction in CL_R (Table 3) that would provide a predicted plasma TXA concentration of 100 - 150 $mg \cdot L^{-1}$ before and during CPB (Fig. 3B). Plasma TXA concentrations were predicted to remain at this threshold for up to 10 h post-surgery in patients with CL_R below 10% of normal (Fig. 3B). It is further known that protein binding that may change with renal dysfunction [18]. The volume of distribution of TXA, however, is expected to remain

unchanged since TXA exhibits minimal protein binding [19]. Hence, changing the loading infusion rate would strongly affected the C_{max} during Phase I but not the steady-state concentration. This was confirmed when we changed the loading dose to a single, high intravenous loading infusion of 50 $mg \cdot kg^{-1}$ (200 $mg \cdot kg^{-1} \cdot h^{-1}$) without giving any maintenance infusion to CRD patients. The predicted initial TXA concentrations were high, and concentrations falling rapidly below the suggested threshold of 100 $mg \cdot L^{-1}$ were observed during and after CPB in patients with > 25% of normal renal function (Fig. 3C).

DISCUSSION

We revisited the works of Sharma [5] and Wąsowicz [14] and coworkers and employed 2-compartment model for pharmacokinetic analysis. Our model was modified/adjusted for use of the extracorporeal compartment (CPB pump circuit) being used during the crucial part of cardiac surgery (Phase III) only; the contents in the CPB circuit were not returned. We found that the compartmental model describes satisfactorily the pharmacokinetics of TXA, especially when the entire data set is used to simultaneously estimate parameters, which were found similar to those of Sharma and coworkers [5]. The modeling demonstrates that the number of samples obtained after discontinuation of infusion exerts no significant impact on the estimation of pharmacokinetic parameters, but their precision was improved with longer sampling, evidenced by the lower CV (Table 1).

Using the combined dataset, effects of the two major covariates: body weight on volume of distribution and clearance, and creatinine clearance on renal clearance, were identified and incorporated into the population pharmacokinetic model. Although a recent study had confirmed that body weight can affect TXA disposition [20], creatinine clearance, in addition to body weight, was identified in our study as having an important impact on TXA pharmacokinetics. After incorporating these two covariates, both the inter-subject variability and OFV were significantly improved, demonstrating that the renal clearance of TXA is associated with both body weight and creatinine clearance, and volume of distribution is linearly related with body weight. Since TXA is a weak acid (pKa of 4.3) that is mostly unbound to plasma proteins [19], non-lipophilic (logP of 0.3) and not reabsorbed , CL_R of TXA approximates GFR, and it is not surprising to find CL_{Cr} as a significant covariate. A similar relationship has been previously described for clearance and volume of distribution of methotrexate, metformin and piperacillin, which are also renally cleared [21-23]. Although it may be argued that data of 15 patients only provided limited population information to

accurately estimate parameters and inter-patient variability, confidence was assured since our estimated %shrinkage values are small and close to zero, the individual prediction and individual estimates should be relatively reliable (Table 2) with respect to covariate identification. If the shrinkage were substantial (> 20%), then the covariate relationship determined in the model might be spurious, and it is harder to detect model misspecification visually by diagnostic plots [24]. It appears that data from all 15 individuals, albeit small, are representative of the patient population.

The identification of creatinine clearance (a reasonable and commonly accepted estimation of GFR in renal function [25]) as a strong determinant of TXA clearance suggests that renally-compromised patients undergoing CPB may require dose-adjustments to offset increased TXA accumulation. High TXA concentrations ($\geq$100 mg·L^{-1}) are associated with seizures in cardiac surgical patients and thrombotic/ischemic complications documented in patients with CRD undergoing prostatectomy [10, 26, 27]. Moderate TXA doses (24 mg·kg^{-1}) given to patients undergoing open-heart surgery have been associated with the risk of post-operative seizures that doubled in-hospital mortality [28]. Although there are several recommended dosing regimens in patients with normal renal function [3, 4, 29-31] (see simulated profiles in Supplemental Fig. 1), the TXA regimen for CRD patients is still unclear. In addition, cardiac surgery studies assessing TXA concentrations among CRD patients undergoing cardiac surgery with use of CPB are scarce, with only one study that described pharmacokinetic model based on a limited number (four) of CRD patients [29].

Simulations clearly demonstrated that the BART dose, if left unchanged, would result in an accumulation of TXA in CPB patients with compromised renal function. According to our simulations based on the compartmental model, the predicted TXA concentrations would be 3-4 times higher for CPB patients with moderate to severe CRD ($\leq$ 25% of normal CL_R), and 4-fold higher for dialysis patients (~1% of normal CL_R) compared to those with normal renal

function (Fig. 3A). The predicted increase in TXA concentrations for CRD patients on the BART infusing regimen could be lowered to the optimal concentration of ~100 $mg \cdot L^{-1}$ with our recommended dosing profile (Table 3), when the maintenance infusion rate was reduced in direct proportion to the %decrease in GFR or CL_R (Fig. 3B). The model further predicted that the prolongation of $t_{1/2\beta}$ is highly correlated to the reduction in CL_R (Fig. 3C).

There has been one other dosing regimen recommended for patients with CRD. This was devised by Fiechtner and coworkers [29], who proposed a 5.4 $mg \cdot kg^{-1}$ loading dose followed by a 5 $mg \cdot h^{-1} \cdot kg^{-1}$ maintenance infusion rate, with 0.5 mg in the CPB circuit during CPB to target TXA concentrations at ~20 $mg \cdot L^{-1}$ for patients with normal renal function. In patients with renal insufficiency, the recommendation was to reduce the maintenance infusion rate to 25%, 50% and 75% of baseline for serum creatinine concentrations above 6, 3.3-6.6 and 1.6-3.3 $mg \cdot dL^{-1}$ respectively [29, 32]. Based on our simulations, however, these recommendations generally yielded TXA concentrations (~30 $mg \cdot L^{-1}$) during CPB that are higher than the proposed 20 $mg \cdot L^{-1}$ (Fig. 4A). For Scr above 6, 3.3-6.6 and 1.6-3.3 $mg \cdot dL^{-1}$, the Cockcroft and Gault equation [33] was used to calculate corresponding CL_{Cr}. Based on the altered CL_{Cr}, our recommendation (matching $\%CL_R$; see Table 4) was arrived. Our recommendations for CRD patients predicted TXA concentrations (25 $mg \cdot L^{-1}$) that are only slightly above the suggested threshold (20 $mg \cdot L^{-1}$) (Fig. 4A), and Fiechtner's infusion rates are 4.9- to 2.4-fold higher than those recommended on the basis of the simulations in this paper (Table 4). For this scenario, the outcome is not serious since the predicted TXA concentrations according to both methods remained below 100 $mg \cdot L^{-1}$. However, when we examined the BART dosing regimen (higher dose) on patients with renal failure, with Scr varying as those described for Fiechtner and coworkers [29], the TXA concentrations predicted based on our recommendations hovered around 150 $mg \cdot L^{-1}$, close to the target value of 100 $mg \cdot L^{-1}$, whereas those for Fiechtner *et al*.'s model [29] could be elevated as high

as 300 $mg \cdot L^{-1}$ (Fig. 4B). In both cases, the infusion rates for Fiechtner *et al*. are 4.9- to 2.4-fold as much as ours. The key implication of this work suggests that reducing the maintenance infusion rate according to $\%CL_R$ and not the loading dose for CRD patients (Tables 3 and 4) in order to maintain TXA at optimal threshold concentrations.

In summary, we showed that the 2-compartment model is robust for estimation of TXA pharmacokinetic parameters regardless of the number of samples obtained after discontinuation of the infusion [5]. We identified two covariates, body weight and creatinine clearance, which affect TXA disposition in cardiac surgical patients operated with use of CPB. Additionally our findings illustrated that simulation methodologies have great potential benefits to patients with impaired kidney function given that TXA is renally filtered, and the technique provides for insight into dosage adjustments that should result in more precise targeting of desired exposure to TXA [34]. Our simulation study has been based on computer modeling and simulations, and proof of the principle needs to be verified clinically to show that our recommendations towards TXA regimen for CRD patients undergoing CPB are sound.

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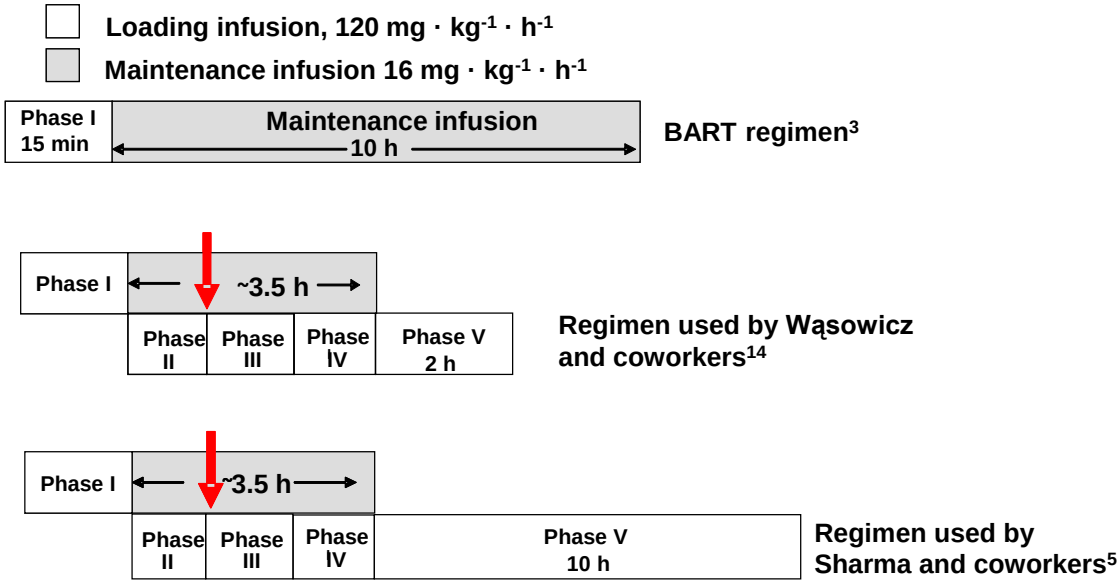
Appendix A



Phase I: 15 min, loading infusion

Phase II: ~ 1 – 1.5 h chest opening

Phase III: ~ 1.8 h, CPB

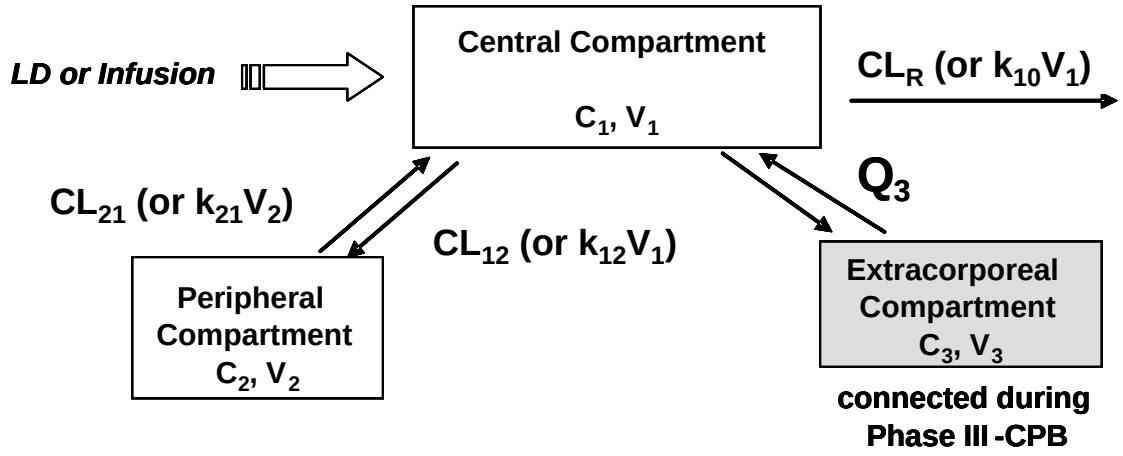
Phase IV: 0.5 h, chest closure

Phase V: washout

Extracorporeal circuit (2 L) containing 2 mg·kg^{-1} bolus for perfusion at 5 L· min^{-1}

The BART regimen [3] was separated into 5 time phases (see figure above), with a 15-min for loading infusion (Phase I) and followed by maintenance infusion (about 10 h). For the regimen of Wąsowicz [14] or Sharma and coworkers [5], the maintenance infusion period was dramatically reduced to ~3.5 h, whereas the sampling times for the study of Wąsowicz and coworkers [14] during Phase V (washout) was about 2 h, and that for Sharma and colleagues [5] was 10 h.

Appendix B



For the protocol that did not return fluids in extracorporeal compartment (CPB pump circuit) back to central compartment, the rate equations are:

$$V_1 \frac{dC_1}{dt} = -(CL_R + CL_{12} + Q_3) \times C_1 + CL_{21} \times C_2 + Q_3 \times C_3 \quad \text{(B1)}$$

$$V_2 \frac{dC_2}{dt} = CL_{12} \times C_1 - CL_{21} \times C_2 \quad \text{(B2)}$$

$$V_3 \frac{dC_3}{dt} = Q_3 \times (C_1 - C_3) \quad \text{(B3)}$$

CL_R (or $k_{10}V_1$) is the renal clearance; CL_{12} (or $k_{12}V_1$) = CL_{21} (or $k_{21}V_2$) are inter-compartmental clearances from central to peripheral compartments and from peripheral to central compartments, respectively; Q_3 is the inter-compartmental flow between central and extracorporeal compartments; V_1, V_2 and V_3 are the volume of central, peripheral and extracorporeal compartments, respectively, and C_1, C_2 and C_3 are the corresponding concentrations. For both ADAPT5® and NONMEM®, time-dependent indicators were set to indicate the two periods: the non-CPB period (Phases I, II, IV, and V) and CPB period (Phase III).

The third compartment was turned on with indicators specifying the time period, as follows:

If (OCC.EQ.0), then $Q_3 = 5\ L \cdot min^{-1}$ (B4)
Else $Q_3 = 0\ L \cdot min^{-1}$
End if
where OCC stands for occasion, the indicator for different periods.

To accommodate return of extracorporeal fluid content to the central compartment, the amount, V_3C_3, is added to that in the central compartment, and the new V_2 is V_2+V_3, at the end of CPB.

Table 1. Parameter estimates for CL_R, CL_{12} or CL_{21}, and V_1 with ADAPT5® from data of Wąsowicz and Sharma and colleagues [5, 14].

Subject[a,b]	**CL_R±CV**[c] **($L \cdot min^{-1}$)**	**V_1±CV (L)**	**CL_{12} or CL_{21}±CV ($L \cdot min^{-1}$)**	**V_2±CV (L)**
1	0.0805±0.116	12.7±0.108	0.0742±0.546	10.4±0.306
2	0.114±0.120	14.4±0.139	0.188±0.738	6.44±0.371
3	0.126±0.179	15.6±0.113	0.0924±0.584	15.1±0.397
4	0.0826±0.128	12.3±0.125	0.0784±0.673	9.31±0.329
5	0.11±0.129	17.0±0.130	0.215±0.601	6.79±0.301
6	0.198±0.132	18.1±0.132	0.217±0.608	10±0.323
7	0.121±0.128	15.1±0.134	0.151±0.703	8.61±0.329
8	0.0833±0.138	12.2±0.139	0.16±0.667	4.76±0.320
9	0.165±0.117	17.4±0.140	0.246±0.708	7.63±0.354
10	0.0896±0.122	11.3±0.144	0.151±0.744	4.97±0.367
Mean ±SEM (n=10)	**0.117±0.386**	**14.6±2.43**	**0.157±0.0607**	**8.4±3.05**
12	0.077±0.080	11.6±0.090	0.0343±0.31	11.9±0.221
14	0.266±0.073	25.8±0.011	0.249±0.398	14.3±0.227
15	0.151±0.072	15.1±0.099	0.0819±0.341	14.1±0.201
16	0.07±0.072	12.8±0.010	0.0973±0.473	7.77±0.241
17	0.151±0.069	16.6±0.139	0.295±0.594	4.69±0.283
Mean ±SEM (n=5)	**0.143±0.0789**	**16.4±5.59**	**0.151±0.114**	**10.6±4.2**
***P* value**[d]	**0.768**	**0.768**	**1.000**	**0.440**
Mean ±SEM (n=15)	**0.126±0.0538**	**15.2±3.67**	**0.155±0.0779**	**9.12±3.49**

[a] Subjects 1-10 were from Wąsowicz and coworkers [14]; subjects 12,14 to 17 were from Sharma and colleagues [5].

[b]The estimated variance parameters are SD_{inter} = 0.00169 and SD_{slope} = 0.302 for the first 10 subjects, and SD_{inter} = 0.00525 and SD_{slope} = 0.35 for the other 5 subjects.

[c] CV (= standard deviation of parameter estimate/ parameter estimate) was much lower for the fit to data of Sharma and coworkers [5]

[d] Mann-Whitney U test was used to compare parameters of first 10 patients (2 samples obtained after TXA infusion stoppage) against those for the other 5 patients (6-8 samples obtained after TXA infusion stoppage).

Table 2. NONMEM results of covariate model building steps to arrive at Model I

Model	Parameter	Covariate Effect	Estimate ± %RSE[a]	Between Subject Variability %BSV± %RSE [%Shrinkage][b]	Residual Variability ± %RSE [%Shrinkage][c]	Total Variability of Model[d]	Minimal OFV[e]
A	CL_R ($L \cdot min^{-1}$)	NA	0.118 ±20.1%	60.3±12.1 [2.20]	0.322± 7.15 [4.76]	1.29	591
	V_1 (L)	NA	16.1 ±7.15%	41.5± 13.3 [2.36]			
	CL_{12} and CL_{21} ($L \cdot min^{-1}$)	NA	0.0839 ±53.8%	105.8±13.2 [22.1]			
	V_2 (L)	NA	13.1 ±7.8%	3.2±12.6 [25.9]			
B	CL_R ($L \cdot min^{-1}$)	$(BW/\overline{BW})^{0.75}$	0.122 ±22.3%	46.9±19.7 [3.36]	0.301± 9.55 [4.71]	1.06	588
	V_1 (L)	$(BW/\overline{BW})$	17.5 ±8.4%	26.9± 19.9 [2.01]			
	CL_{12} and CL_{21} ($L \cdot min^{-1}$)	$(BW/\overline{BW})^{0.75}$	0.0820 ±129.9%	89.2±18.1 [18.9]			
	V_2 (L)	$(BW/\overline{BW})$	6.6 ±121%	19.3±19.5 [10.3]			
C	CL_R ($L \cdot h^{-1}$)	$(BW/\overline{BW})^{\Theta 1}$	0.131 ±11.2%	33.2±22.5 [1.15]	0.237±3.81 [4.40]	1.22	582
	Θ_1[f]		3.28 ±9.61%	N.A.			
	V_1 (L)	$(BW/\overline{BW})$	20 ±10.6%	29.8±19.9 [2.63]			
	CL_{12} and CL_{21} ($L \cdot h^{-1}$)	$(BW/\overline{BW})^{\Theta 2}$	0.0863 ±1.04%	3.20±20.0 [3.92]			
	Θ_2[f]		0.325 ±3.66%	N.A.			
	V_2 (L)	$(BW/\overline{BW})$	12.6 ±39.8%	114±22.3 [5.49]			
D	CL_R ($L \cdot h^{-1}$)	$(BW/\overline{BW})^{\Theta 1}$	0.124 ±11.3%	43.2±17.7 [1.49]	0.332±5.15 [4.41]	0.726	552
	Θ_1		1.27 ±21.0%	N.A.			
	V_1 (L)	$(BW/\overline{BW})$	12.8 ±8.16%	26.1±17.1 [2.08]			
	CL_{12} and CL_{21} ($L \cdot h^{-1}$)	$(BW/\overline{BW})^{\Theta 2}$	0.0968 ±15.2%	N.A.			
	Θ_2		1.12 ±1.40%	52.1±18.4 [3.49]			
	V_2 (L)	N.A.	8.86 ±1.08%	3.33±17.8 [2.02]			
E	CL_R ($L \cdot h^{-1}$)	$(CL_{Cr}/\overline{CL_{cr}})^{\Theta 1}$	0.134 ±13.4%	41.7±10.8 [1.55]	0.338±3.67% [4.41]	0.579	573
	Θ_1		0.429 ±25.6%	N.A.			
	V_1 (L)	N.A.	13.2 ±10.4%	31.9±12.0 [2.05]			
	CL_{12} and CL_{21} ($L \cdot h^{-1}$)	$(CL_{Cr}/\overline{CL_{cr}})^{\Theta 2}$	0.0650 ±4.59%	12.2±12.7 [3.55]			
	Θ_2		1.89 ±2.20%	N.A.			
	V_2 (L)	N.A.	5.86 ±10.6%	21.2±13.9 [4.95]			
F	CL_R ($L \cdot h^{-1}$)	$Exp(\Theta_1 * (CL_{Cr}/$	0.071	46.3±18.4	0.323±3.37	0.839	582

		$\overline{CL_{cr}}$))	±27.2%	[3.19]	[6.38]		
	Θ_1	.	0.558 ±20.4%	N.A.			
	V_1 (L)	N.A.	14.4 ±8.16%	35.5±10.3 [12.6]			
	CL_{12} and CL_{21} (L·h^{-1})	Exp(Θ_2*(CL_{Cr}/ $\overline{CL_{cr}}$))	0.0825 ±23.8%	21.3±18.0 [28.9]			
	Θ_2		1.02 ±8.41%	N.A.			
	V_2 (L)	N.A.	7.54 ±18.6%	56.4±18.4 [23.7]			
G	CL_R (L·h^{-1})	(CL_{Cr}/ $\overline{CL_{cr}}$)$^{\Theta_1}$	0.137 ±13.4%	43.2±17.7 [1.06]	0.332±5.15 [4.41]	0.726	562
	Θ_1		1.37 ±6.1%	N.A.			
	V_1 (L)	(BW/ $\overline{BW}$)	19 ±8.47%	26.1±71.0 [1.69]			
	CL_{12} and CL_{21} (L·h^{-1})	(BW/ $\overline{BW}$)$^{\Theta_2}$	0.0767 ±15.3%	52.1±28.0 [3.49]			
	Θ_2		1.22 ±26.1%	N.A.			
	V_2 (L)	N.A.	7.6 ±1.08%	3.3±17.8 [3.48]			
H	CL_R (L·h^{-1})	(CL_{Cr}/ $\overline{CL_{cr}}$)$^{\Theta_1}$	0.120 ±16.8%	45.5±11.6 [1.75]	0.314±3.5 [4.1]	0.937	546
	Θ_1		0.86 ±13.6%	N.A.			
	V_1 (L)	(BW/ $\overline{BW}$)	14.9 ±6.81%	3.1±12.0 [2.04]			
	CL_{12} and CL_{21} (L·h^{-1})	(CL_{Cr}/ $\overline{CL_{cr}}$)$^{\Theta_2}$	0.0867 ±20.0%	80.9±12.7 [3.38]			
	Θ_2		1.06 ±16.4%	N.A.			
	V_2 (L)	N.A.	12.3 ±8.54%	12.8±12.7 [3.75]			
I	CL_R (L·h^{-1})	(BW/ $\overline{BW}$)$^{\Theta_{1*}}$ (CL_{cr}/ $\overline{CL_{cr}}$)$^{\Theta_2}$.	0.116 ±16.7%	38.0±17.3 [1.01]	0.332±3.73 [4.01]	0.478	517
	Θ_1		0.0445 ±15.3%	N.A.			
	Θ_2		1.21 ±16.9%	N.A.			
	V_1 (L)	(BW/ $\overline{BW}$)	17.3 ±5.37%	21.4±19.6 [2.39]			
	CL_{12} and CL_{21} (L·h^{-1})	(CL_{cr}/ $\overline{CL_{cr}}$)$^{\Theta_3}$	0.0110 ±13.3%	19.4±17.6 [4.22]			
	Θ_3		-0.607 ±11.5%	N.A.			
	V_2 (L)	N.A.	9.5 ±10.6%	1.5±19.4 [4.01]			

[a] SEM/parameter estimate

[b] %Shrinkage for between- or inter-subject variability, if substantial (>30%), is suggestive that covariates might be falsely introduced or the covariate relationship is spurious;

if %Shrinkage is ~0, then estimated parameter and incorporated covariate relationship are relatively more reliable.

[c] Residual variability is the remaining, random variability, after adjustment for inter-subject variability (and/or inter-occasion variability).

[d] Sum of between- or inter-subject variability for each of the parameters, or $[\sum\eta^2(CL_R+V_1+Q_2+V_2)]^{1/2}$, where η denotes BSV, or variability of parameter estimate

[e] Objective function value, parameter that indicates improved model fit; the lower the value, the better the fit

[f] Fitted exponent, and not the assigned 0.75 exponent, for allometric scaling

Table 3. Reduction of maintenance infusion rate (MD) for conditions of reduced CL_R

	%GFR or %CL_R						
	100%	**75%**	**50%**	**25%**	**10%**	**5%**	**1%**
CL_R[a] ($L \cdot min^{-1}$)	0.116	0.0868	0.0581	0.0287	0.119	0.0056	0.0014
Maintenance Infusion (MD) Rate ($mg \cdot h^{-1} \cdot kg^{-1}$)	16	12[a]	6[a]	5[a]	1.6[a]	0.8[a]	0.16[a]

[a]Pharmacokinetic parameters were presented in terms of a standard individual with body weight of 70 kg.
[b]Estimated as %GFR multiplied to the starting maintenance dose of 16 $mg \cdot h^{-1} \cdot kg^{-1}$

Table 4 Recommended dosing regimen by Fiechtner and our study to maintain plasma TXA concentrations of 20 $mg \cdot L^{-1}$.

Fiechtner and coworkers recommended reduction in maintenance infusion rate (MD) based on Scr [29], whereas ours was based on upon converting Scr to CL_{Cr} (or CL_R) using the Cockcroft-Gault equation [33]; our recommended change in MD equaled $\%CL_R$ x normal MD. Fiechtner and colleagues used a loading dose of 5.4 $mg.kg^{-1}$, and MD 5 $mg.kg^{-1}.h^{-1}$ for patients with normal renal function. The MD of Fiechtner and coworkers [29] were 2.4- to 4.9-fold our recommendations (see table below):

Scr ($mg \cdot dL^{-1}$)	%Reduction in MD suggested by Fiechtner and coworkers[a]	CL_{Cr} ($\%CL \bullet min^{-1}$)[b] Estimated Based on Scr		$\%CL_{Cr}$/GFR[c] %Reduction in CL_R =%Reduction in MD[d]	Ratio of Maintenance Infusion (MD) Rates (Fiechtner/ our recommendation)
		Female	Male		
>6.6	25	0-13.8	0-11.7	5.1	4.9
3.3-6.6	50	13.8-27.5	11.7-23.4	15.4	3.25
1.6-3.3	75	27.5-56.7	23.4-48.2	31.4	2.39

[a] Suggested by Fiechtner and coworkers [29] for the given Scr

[b] CL_{Cr} values were estimated with the Cockcroft-Gault equation [33], assuming BW = 86 kg, age= 64 for both sexes.

[c] CL_{Cr} / GFR (110 $mL \cdot min^{-1}$ for females and 140 $mL \cdot min^{-1}$ for male), and values were averaged

[d] We recommend maintenance infusion to match $\%CL_R$ of normal.

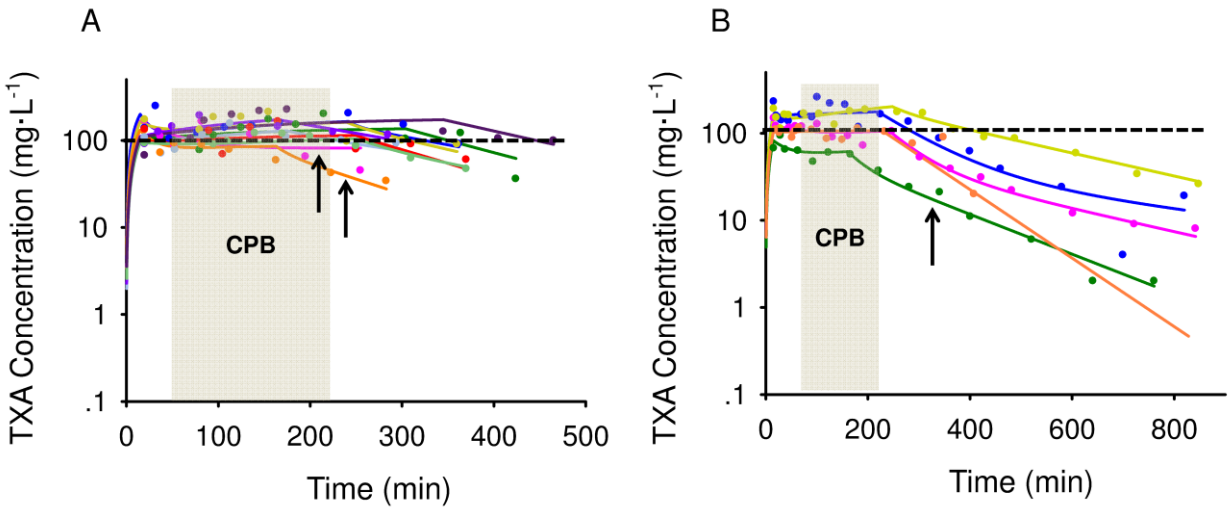


Fig.1 Fitted (solid lines) and observed (solid symbols) TXA concentrations versus time plots for (A) shorter and (B) longer sampling time. For these data sets, pump fluids containing TXA were not returned to patients at the end of CPB. Each patient is marked by a different color, and the grey shaded area represents the CPB period. The dotted black line demarcates the suggested concentration (100 mg·L^{-1}) for 100% anti-fibrinolytic effect of TXA. Three patients show TXA concentrations consistently lower than the suggested threshold, indicated by the black arrows.

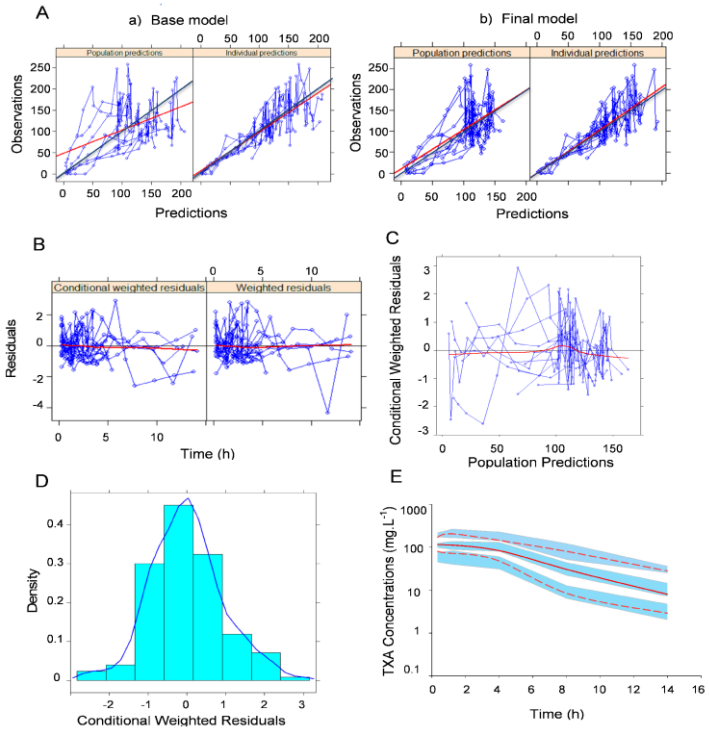


Fig. 2 Plots showing improvement of model predictability based on observed vs. individual and population predicted concentration profiles from (A) the basic (a) to the final (b) model [red line is regression line and the blue line is the line of identity]**, and diagnostic plots (B)-(F) for the final model, Model I: (B) and (C)** show the distribution of conditional weighted residuals (CWRES) vs. time and vs. population prediction, respectively; these data hovered around the y=zero line, showing goodness of fit, and **(D)** shows the test of normality of frequency vs. CWRES, with the mean=1 and variance of CWRES=0, respectively, by the Wilcoxon signed rank test (P = .31), Fisher's variance test (P = .53), and the Shapiro-Wilk test of normality; the data show that CWRES follows a normal distribution (P = .71); **(E)** the visual predictive check, plot was generated by NONMEM $simulation based on the final model I, suggests that the final model has good precision relative to the variation contained in the raw observation. The solid and dashed red lines represent the median and 5% and 95% quartiles of observed data, respectively, and the semitransparent blue fields are the corresponding 90% confidence intervals. The solid and dashed red lines denote the median, 5% and 95% quartiles of observed data, respectively.

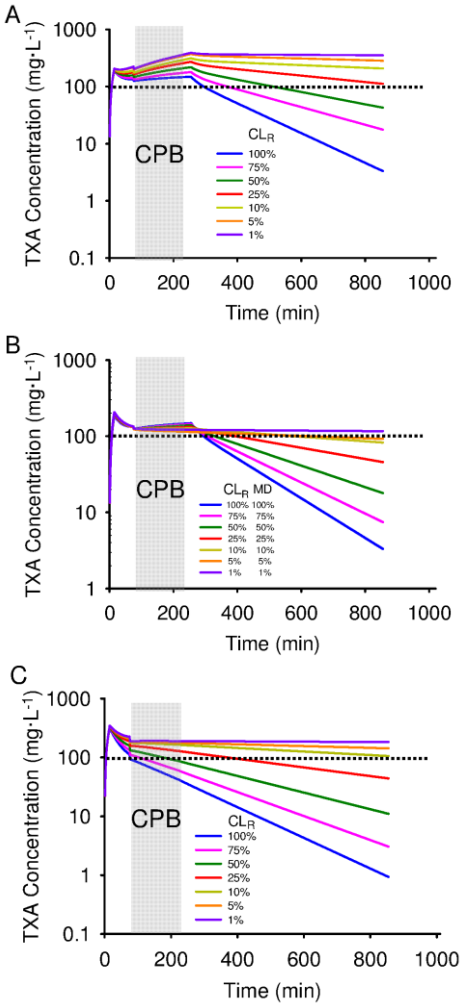


Fig. 3 Simulated TXA concentration vs. time profile with (A) no adjustments in the BART regimen to CRD patients; (B) %reduction of maintenance infusion dose (MD) proportionally to the %reduction in CL_R of CRD patients; and (C) a single loading dose of 200 mg·kg^{-1}·h^{-1} (50 mg·kg^{-1}) in CRD patients. For these simulations, pump fluids containing TXA were returned to patients at the end of CPB. The different severity of CRD is represented by reducing renal clearance values (CL_R) according to different percentage (75, 50, 25, 10, 5, and 1%) of normal CL_R. The grey shaded area represents the CPB period and the dotted black lines represent the suggested concentration (100 mg·L^{-1}) allowing 100% anti-fibrinolytic effect of TXA.

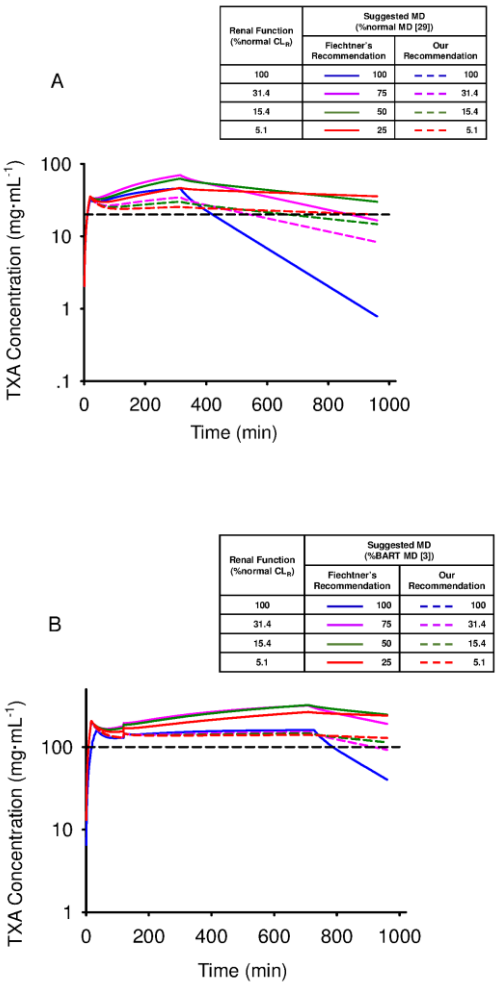


Fig. 4 TXA concentration vs. time profiles simulated according to the two-compartmental model (with return of CPB contents) using Fiechtner's recommendation [29] (solid line) as well as our recommendations (dashed line) based on reduction of the maintenance infusion dose (MD), when the serum creatinine concentration (Scr) was converted to %CL_R according to the Cockcroft-Gault equation [33] for targeting 20 mg·L^{-1} (A) or 100 mg·L^{-1} (B). For (B), the dosing regimen in BART trial [3] was used. See text for details. Notably, our recommendation provided simulated TXA concentrations closer to the 20 and 100 mg·L^{-1} targets, compared to those of Fietchner and coworkers [29].