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Pharmacokinetics of Tranexamic Acid during Cardiopulmonary Bypass

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Background: **Tranexamic acid (TA) reduces blood loss and blood transfusion during heart surgery with cardiopulmonary bypass (CPB). TA dosing has been empiric because only limited pharmacokinetic studies have been reported, and CPB effects have not been characterized. We hypothesized that many of the published TA dosing techniques would prove, with pharmacokinetic modeling and simulation, to yield unstable TA concentrations.**

Methods: **Thirty adult patients undergoing elective coronary artery bypass grafting, valve surgery, or repair of atrial septal defect received after induction of anesthesia: TA 50 mg/kg (n = 11), TA 100 mg/kg (n = 10), or TA 10 mg/kg (n = 10) over 15 min, with 1 mg · kg^{-1}· hr^{-1} maintenance infusion for 10 h. TA was measured in plasma using high performance liquid chromatography. Pharmacokinetic modeling was accomplished using a mixed effects technique. Models of increasing complexity were compared using Schwarz-Bayesian Criterion (SBC).**

Results: **Tranexamic acid concentrations rapidly fell in all three groups. Data were well fit to a 2-compartment model, and adjustments for CPB were supported by SBC. Assuming a body weight of 80 kg, our model estimates V_1 = 10.3 l before CPB and 11.9 l during and after CPB; V_2 = 8.5 l before CPB and 9.8 l during and after CPB; Cl_1 = 0.15 l/s before CPB, 0.11 l/s during CPB, and 0.17 l/s after CPB; and Cl_2 = 0.18 l/s before CPB and 0.21 l/s during and after CPB. Based on simulation of previous studies of TA efficacy, we estimate that a 30-min loading dose of 12.5 mg/kg with a maintenance infusion of 6.5 mg · kg^{-1}· hr^{-1} and 1 mg/kg added to the pump prime will maintain TA concentration greater than 334 μM, and a higher dose based on 30 mg/kg loading dose plus 16 mg·kg^{-1} ·h^{-1} continuous infusion and 2 mg/kg added to the pump prime would maintain TA concentrations greater than 800 μM.**

Conclusions: **Tranexamic acid pharmacokinetics are influenced by CPB. Our TA pharmacokinetic model does not provide support for the wide range of TA dosing techniques that have been reported. Variation in TA efficacy from study to study and confusion about the optimal duration of TA treatment may be the result of dosing techniques that do not maintain stable, therapeutic TA concentrations.**

TRANEXAMIC acid (TA) has been shown to significantly reduce blood loss and red blood cell transfusion rates in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB).[1–3] TA inhibits fibrinolysis, a putative mechanism of bleeding after CPB, by forming a reversible complex with plasminogen.[4] The optimum dose of TA for this purpose is debated in the literature, and the doses of TA used in reported studies vary over a 10-fold range. Some dosing schedules were based on doses previously determined to inhibit plasma fibrinolytic activity[5] in settings outside cardiac surgery; others were developed empirically. However, all dosing schedules were chosen without knowledge of TA elimination kinetics in surgical patients undergoing CPB. All previous studies of the pharmacokinetics of intravenous TA have concentrated on healthy volunteers,[6,7] patients with chronic renal disease,[8] or older patients undergoing total hip arthroplasties.[9] It is likely that CPB will interfere with the elimination kinetics and blood concentration of TA, since such CPB-related effects have been found with ε-aminocaproic acid, a closely related compound.[10,11]

The aim of this study was to examine the effects of CPB on TA plasma concentrations and elimination kinetics using the most commonly accepted dosing schemes of TA. We hypothesized that TA elimination would be greatly reduced during CPB relative to times before and after CPB. We prospectively measured plasma TA concentrations during and after CPB using high performance liquid chromatography (HPLC), subjected those measurements to pharmacokinetic modeling, and tested the effect of CPB on model fits. Finally, we simulated a series of published TA dosing schemes to determine whether they produced stable TA concentrations in plasma.

Materials and Methods

After receiving institutional ethics committee approval and written informed patient consent, 32 adult men or women patients, aged 30–65 yr with normal renal function (serum creatinine of 70–130 μM/l and no clinical history of renal disease) undergoing elective coronary artery bypass grafting, valve surgery, or repair of atrial septal defect, were enrolled in the study. Patients undergoing repeat cardiac surgery, double valve procedures, combined aortocoronary bypass and valve procedures or valve replacement for septic endocarditis, and patients with renal impairment (creatinine > 130 μM), a hemoglobin level less than 120 g/l, or an allergy to study medication were excluded. All patients underwent surgery at the Toronto General Hospital.

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Patients were randomly assigned to receive one of three doses of TA: Group TA 50 (n = 11), received a single bolus of TA 50 mg/kg intravenously over 15 min starting after induction of anesthesia (using an infusion pump); Group TA 100 (n = 10), received TA 100 mg/kg, intravenously over 15 min (using an infusion pump) starting after induction of anesthesia; and Group TA 10 (n = 10), received a loading dose of TA 10 mg/kg intravenously over 15 min (using an infusion pump) starting after induction of anesthesia followed by an infusion (using an infusion pump) of 1 $mg \cdot kg^{-1} \cdot hr^{-1}$ for 10 h. These particular doses of TA were chosen based on our previous published TA efficacy data as well as data published by Horrow *et al.*[1,2,12] TA was administered as a "piggy-back" infusion in a freely-flowing intravenous line.

Preoperative sedation consisted of lorazepam 1 to 2 mg sublingually approximately 1.5 h before surgery. Peripheral and radial artery cannulae were placed after local anesthesia. General anesthesia was induced with 10–15 μg/kg fentanyl, and in some cases, 50–75 mg thiopental intravenously. Tracheal intubation was facilitated by intravenous pancuronium 0.15 mg/kg. Anesthesia was maintained before cardiopulmonary bypass (CPB) with midazolam 0.05–0.1 mg/kg, a propofol infusion at 2–6 $mg \cdot kg^{-1} \cdot hr^{-1}$, and in some cases, 0.5–2% inhaled isoflurane. The propofol infusion was continued during CPB at 2–6 $mg \cdot kg^{-1} \cdot hr^{-1}$ and was reduced to 2 $mg \cdot kg^{-1} \cdot hr^{-1}$ before transportation to the intensive care unit (ICU). It was continued for 3 h in ICU at 0.5–3 $mg \cdot kg^{-1} \cdot hr^{-1}$. Anticoagulation for CPB was provided by heparin 300 U/kg. An activated clotting time (ACT) of greater than 400 s was achieved before CPB, and maintained with additional heparin as indicated by the ACT during CPB. After CPB, protamine sulfate 1 mg/100 U of heparin administered was given to restore the ACT to within 10% of its baseline value. Protamine sulfate 50–100 mg was administered after admission to the ICU if the ACT exceeded 110% of its baseline value.

A standard surgical technique was used for all patients. The CPB circuit was primed with 2 l of Ringer's lactate, 100 ml of 25% albumin, 50 mEq of sodium bicarbonate, and 100 ml of mannitol. Systemic temperature was allowed to drift to 33°C during CPB. Roller pumps and membrane oxygenators (Maxima Medtronic Inc., Minneapolis, MN) were used in all cases. Hematocrit concentrations were maintained between 20–25% and CPB flow rate between 2.0–2.5 $l \cdot min^{-1} \cdot m^{-2}$. Patients were actively rewarmed to a nasopharyngeal temperature of 38°C before weaning from CPB.

Cold (10°C) or tepid (29°C) antegrade or retrograde blood cardioplegia was used for myocardial protection according to surgeon preference. Our cardioplegic consisting of oxygenated blood mixed with crystalloid in an 8:1 ratio to achieve a final concentration of 6 mEq/l of magnesium sulfate, 50 mM of glucose, and either a small (8 mEq/l) or large (27 mEq/l) concentration of potassium chloride.

Blood was transfused during CPB when the hematocrit was less than 19%. The blood remaining in the circuit after discontinuation of CPB was salvaged and transfused to the patient after sternal closure. Postoperatively, mediastinal and chest drains were connected to a citrated sterile cardiotomy reservoir. When drainage of blood exceeded 150 ml in the first 6 h, it was autotransfused to the patient.

A set of timed arterial blood samples (5 ml) was obtained from each patient in Group TA 50 and group TA 100 as follows:

1. Before giving the drug, and 2, 4, 6, 10, 30, 60, 90, 180, 400, and 600 min after the drug infusion was completed,
2. Immediately before and 5 min after initiation of CPB, and
3. 24 h after the drug was given.

In Group TA 10, blood (5 ml) was sampled at the following time points:

1. Before giving the drug, and 2, 4, 6, 10, 30, 60, 90, and 180 min after completion of the loading dose,
2. Exactly as the maintenance infusion was stopped and at 2, 5, 10, and 60 min after the infusion finished, and
3. 24 h after the drug was given.

The blood samples were immediately anticoagulated with ethylene diamine tetraacetic acid and stored on ice. Plasma was separated by centrifugation (1,000 g × 10 min at 4°C) and stored at −70°C pending analysis for TA concentrations. Frozen plasma samples were packed in dry ice and shipped from Toronto, Ontario, Canada to Winston-Salem, North Carolina, for measurement of plasma concentrations and pharmacokinetic analysis. Plasma concentration was analyzed by high-performance liquid chromatography after ultrafiltration and derivatization (Appendix).

Statistical Methods

Concentration *versus* time data were fit to compartmental models using the nonlinear mixed effects regression techniques of the NONMEM software package (NONMEM Project Group, University of California, San Francisco, CA). These pharmacokinetic models were fit by:

$$\text{Objective function} = \sum\left[\frac{(C_i - \hat{C}_i)^2}{Var_i}\right] + \ln (Var_i)$$

minimizing the extended least squares. Extended least squares nonlinear regression uses the following maximum likelihood objective function: where C_i = observed EACA concentration at time i, C_i = predicted (from model EACA concentration at time i, and var_i =

expected variance at time i. The expected variance at time i includes terms reflecting both intra- and interpatient variability. The intrapatient variability (error) was modeled as a power function, using either a constant coefficient of variation (CV), or a combined additive and CV (Add + CV) model.[13] For any specified model, the set of parameter estimates that minimizes the objective function is considered the best fit. Model fits were graphed over the assay data to confirm that the fits were reasonable.

First order (FO) estimations were used initially in NONMEM to fit the models. However, the LaPlacian and FOCE estimation methods (requiring much longer computer times) were tried whenever NONMEM had difficulty fitting a particular model using FO methods. LaPlacian estimation methods were also used as a final check on our best FO estimated models.

Model rate constants, k_{10}, k_{12}, k_{21}, k_{13}, and k_{31}, and the central compartment's volume of distribution, V_1, were estimated directly by the NONMEM program. Clearances and the remaining compartment volumes of distribution were calculated from the rate constants as follows: $Cl_{10} = V_1 \cdot k_{10}$, $Cl_{12} = V_1 \cdot k_{12}$, and $V_2 = k_{12} \cdot V_1/k_{21}$. Parameter subscripts refer to the model's compartment number. Double subscripts refer to flow from one compartment to the next (*e.g.*, k_{12} is the rate constant describing drug movement from compartment 1 to compartment 2). Compartment 0 is outside the body.

The mixed effects interpatient variability of the rate constants and V_1 was assumed to be lognormal in distribution and was modeled by NONMEM as follows:

$$\theta_{ij} = \theta_i e^{\eta_{ij}}$$

where the subscript "i" refers to the model parameter and "j" indicates an individual patient, θ_{ij} = parameter estimate of individual patients j, θ_i = population parameter estimate, η_{ij} = random variable normally distributed with mean 0 and variance Ω_i that accounts for interpatient variability associated with the patient.

We attempted to fit pharmacokinetic models as 1-, 2-, and 3-compartment models with and without the demographic covariates: age, sex, height, weight, body surface area, body mass index, and preoperative creatinine concentration. Model parameters were fit in our various models as both linear and quadratic functions of these covariates. Possible covariate models were tested by first selecting the obvious covariate models based on previous modeling experience and intuition. These tested covariate models included adjusting V_1, k_{10} for body weight, BMI, sex, and CPB. Then, to insure that other possible covariate relationships have not been missed, *post hoc* Bayesian estimates of individual η values from our best models both with and without previously fit covariates were plotted. When there was any hint of a relationship between the ηs of a model parameter and a covariate, then parameter adjustments using that covariate would be tested in the model.

Time-dependent indicator covariates indicating three perioperative phases (pre-CPB, CPB, and post-CPB) were included in some model fits. These indicator covariates change from 0 to 1 during the different perioperative phases. For example, the elimination rate constant, k_{10}, can be modeled with indicator covariate, I_{CPB}, as follows:

$$k_{10} = \theta_1 + \theta_2 \cdot I_{CPB}$$

where: θ_1, θ_2 are model estimated parameters,

$$I_{CPB} = \begin{cases} 0: & \text{during pre- and post-CPB} \\ 1: & \text{during CPB} \end{cases}$$

this results in:

$$k_{10} = \theta_1 \text{ pre- and post-CPB}$$

$$k_{10} = \theta_1 + \theta_2 \text{ during CPB}$$

Thus, as shown above, k_{10} can be modeled to increase by θ_2 during CPB. If k_{10} does not change during CPB the best model's estimate of θ_2 will not differ statistically from 0 (*i.e.*, the 95% confidence limit of &thetas;$_2$ will include 0). In similar manners, indicator covariates can be added for the pre-CPB, or post-CPB phases.

Dosing group indicator covariates were also added to some models to confirm the usual pharmacokinetic assumption of dose-independent kinetics. For example:

$$k_{10} = \theta_1 + \theta_2 \cdot I_{high}$$

where θ_1, θ_2 are model estimated parameters,

$$I_{high} = \begin{cases} 0\text{: for observations from patients} \\ \quad \text{receiving the 50 mg/kg bolus infusion} \\ 1\text{: for observations from patients} \\ \quad \text{receiving the 100 mg/kg bolus infusion} \end{cases}$$

We also tested model fits when data from the lowest dose group (TA 10) were excluded. Thus, if k_{10} is not dose-dependent then + θ;$_2$ should not differ statistically from 0.

The Schwarz-Bayesian criterion (SBC) was used to determine which models best fit the data. Models that NONMEM was either unable to determine standard errors for or whose confidence intervals included zero were excluded. Graphs showing model fits were used to confirm our choice of best model.

As a single measure of overall model performance, we presented the seventy-fifth, ninetieth, and ninety-fifth percentiles of the geometric performance error (GPE). The GPE for each sample is equal to the antilog (log(observed) − log(predicted)). Differences on the logarithmic scale become ratios on the arithmetic scale. Thus, a

Table 1. Characteristics of Patients Completing the Study

Group	Age (yr)	BSA (m^2)	CPB Duration (min)	Valve (n)	Type of Surgery		Preop Serum Creatinine (μM/l)
					Coronary Artery (n)	Atrial Septal Defect (n)	
TA 50 (n = 10)*	55 ± 4	1.8 ± 0.02	83 ± 10	0	9	1	71 ± 3
TA 100 (n = 10)†	57 ± 4	1.9 ± 0.02	75 ± 9	1	7	2	82 ± 4
TA 10 (n = 10)	55 ± 6	1.8 ± 0.01	73 ± 10	0	9	1	80 ± 6

Data are presented as mean ± SEM.

* One additional patient with atrial septal defect was enrolled, but excluded because of protocol violation.

† One additional patient having coronary artery surgery was enrolled, but excluded because of perioperative cardiac arrest.

BSA = body surface area; CPB = cardiopulmonary bypass; Preop = preoperative; TA = tranexamic acid.

model with a seventy-fifth percentile of GPE = 1.5 means that 75% of the model predicted concentrations are within a factor of 1/1.5 and 1.5 times (*i.e.*, within 67% and 150%) of the observed concentration.

Simulations using our best CPB-adjusted pharmacokinetic model were performed to predict expected TA concentrations for several previously published dosing schemes. Through trial and error, we also derived a dosing scheme that maintained TA concentrations near Horrow's therapeutic threshold concentrations.[12] Simulations were performed using NONMEM. For simulation purposes, we assumed a patient weight of 80 kg, and 45 min of surgery before and after 120 min of CPB.

All analyses were accomplished using either NONMEM or the SAS Program, version 8.0 (SAS Institute, Cary, NC) with $\alpha < 0.05$ considered significant.

Results

Patient demographic characteristics are presented in table 1. There were no notable differences comparing the three dose groups. There were no adverse events attributable to the use of TA in any of these patients. One patient was excluded from the TA 50 group for a protocol violation, and one patient experiencing intraoperative cardiac arrest was excluded from the TA 100 group.

Peak plasma concentrations were much higher in groups TA 50 and TA 100 than in group TA 10 (fig. 1A–C). TA was rapidly eliminated in all three groups. Despite the maintenance infusion, TA concentrations in group TA 10 steadily declined during the course of surgery. We found no evidence for dose-dependent pharmacokinetics.

Using the NONMEM program and the Schwarz-Bayesian Criterion, we determined that a 2-compartment model was more efficient than a 1-compartment model, so 2-compartment model estimates are reported (table 2). We attempted to fit 3-compartment models to our data, but were unable to find a 3-compartment model that fit our data. When we attempted to fit 3-compartment models, the usual error reported by NONMEM was: "k_{21} or k_{31} too close to an eigen value." The best 2-compartment model fit based on the SBC group included reduction of the elimination rate constant k_{10} during CPB, and an increase in V_1 during and after CPB (tables 3, 4). The elimination rate constant declined significantly from 0.017 before CPB to 0.010 during CPB. Volume of

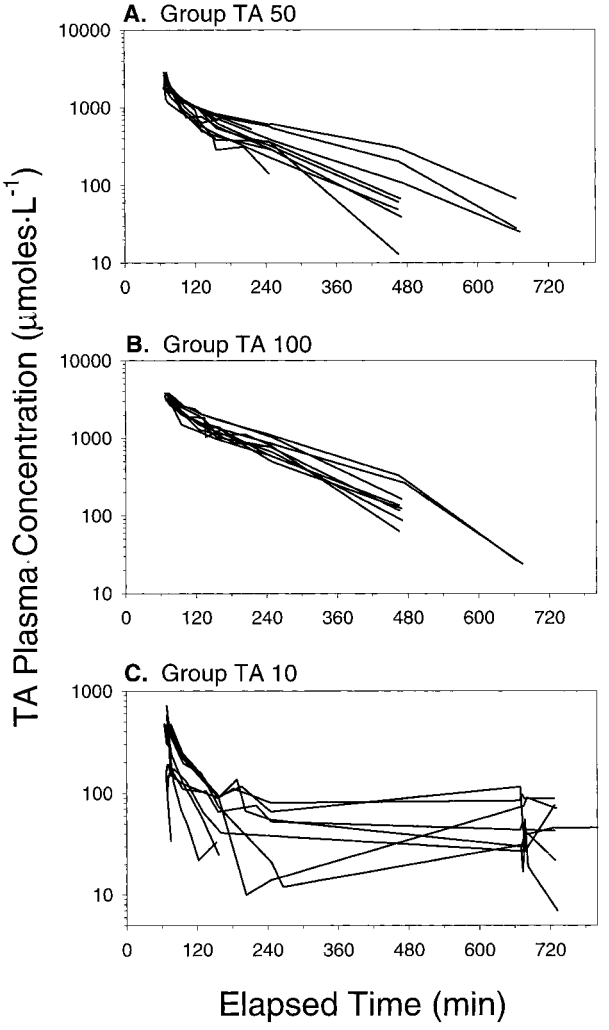

Fig. 1. (*A*) Tranexamic acid (TA) concentrations in blood after a 50 mg/kg loading dose was given intravenously over 15 min after induction of anesthesia. (*B*) TA concentrations in blood after a 100 mg/kg loading dose was given intravenously over 15 min after induction of anesthesia. (*C*) TA concentrations in blood after a 10 mg/kg loading dose was given intravenously over 15 min after induction of anesthesia, and a 1 mg · kg^{-1} · hr^{-1} maintenance infusion was given for 10 h.

Table 2. Fit Criteria of Selected Models Fit to Our Data Using NONMEM

Model Description	Parameters (Fixed)	Intraindividual Error	Objective Function (Smaller is Better)	SBC (Larger is Better)	GPE Percentiles (Smaller is Better)		
					75th	90th	95th
1 Compartment	$k_{10} = \theta_1$ $V_1 = \theta_2$*wtkg	Add + CV $C_i = \varepsilon_{1i} + \varepsilon_{2i} \cdot \hat{C}_i$	3486.472	−1760.4	1.93	3.64	6.83
2 Compartment	$k_{10} = \theta_1$ $k_{12} = \theta_2$ $k_{21} = \theta_3$ $V_1 = \theta_4$*wtkg	Add + CV $C_i = \varepsilon_{1i} + \varepsilon_{2i} \cdot \hat{C}_i$	3318.895	−1688.1	1.64	2.40	3.85
2 Compartment	$k_{10} = \theta_1$ $k_{12} = \theta_2$ $k_{21} = \theta_3$ $V_1 = \theta_4$*wtkg	Power function $C_i = \varepsilon_{1i} \cdot \hat{C}_i^{\xi}$	3322.408	−1689.9	1.63	2.30	3.67
2 Compartment, CPB adjustments	$k_{10} = \theta_1 + \theta_6$*$I_{CPB}$ $k_{12} = \theta_2$ $k_{21} = \theta_3$ $V_1 = \theta_4$*wtkg + θ_5*$I_{pre\text{-}CPB}$	Add + CV $C_i = \varepsilon_{1i} + \varepsilon_{2i} \cdot \hat{C}_i$	3314.231	−1691.5	1.65	2.35	3.41
2 Compartment,* CPB adjustments	$k_{10} = \theta_1 + \theta_6$*$I_{CPB}$ $k_{12} = \theta_2$ $k_{21} = \theta_3$ $V_1 = \theta_4$*wtkg + θ_5*$I_{pre\text{-}CPB}$	Power function $C_i = \varepsilon_{1i} \cdot \hat{C}_i^{\xi}$	3286.134	−1677.5	1.62	2.28	3.37

* Our best model to fit the data.

SBC = Schwarz-Bayesian Criterion; $\theta_1, \ldots, \theta_7$ = model population parameters fit by NONMEM; $\hat{C}_i$ = model predicted plasma TA concentration for sample i; C_i = observed plasma TA concentration for sample i;

$$I_{CPB} = \begin{cases} 0: & \text{before and after CPB} \\ 1: & \text{during CPB;} \end{cases}$$

$$I_{pre\text{-}CPB} = \begin{cases} 0: & \text{during and after CPB} \\ 1: & \text{before CPB;} \end{cases}$$

ε_{1i}, ε_{2i} = random variable error terms for sample i with means = 0 and SD σ_1 and σ_2, respectively. GPE = geometric performance error. In our best model,* 90th GPE = 2.28 means that 90% of our model predictions fell within 1/2.28 and 2.28 times (*i.e.*, 44% and 228% of) the observed concentrations.

Add = additive; CV = coefficient of variation; CPB = cardiopulmonary bypass; wtkg = weight in kg.

distribution increased by 1.61 l at onset of CPB and remained at this level afterwards. The effect of these adjustments on the relationship between observed and predicted TA concentrations is illustrated in figure 2.

We have modeled the concentrations that would be produced by a number of published TA dosing schemes (fig. 3). Several of these dosing schemes are notable for the unstable concentrations that they produce. For comparison, we have modeled the series of TA doses tested by Horrow *et al*. in their efficacy trial, and on all other simulations have included a simulation of the lowest dose that Horrow *et al*.[12] found to reduce bleeding. Our simulation of Horrow's[12] lowest efficacious dosing scheme found a peak concentration of 334 μM for the typical patient occurring at the termination of the loading dose.

Using our mixed-effects model with adjustments for CPB, we have calculated three dosing techniques that target (in the typical patient) an intraoperative TA concentration of 800 μM, 334 μM, or 210 μM, depending on whether the peak concentration or the concentration present at initiation of CPB (with the one time dosing[12] technique) should be maintained (fig. 4). This recommendation is based on our work and the work of Horrow *et al*.[12] in which various doses of TA were compared for efficacy. We assume that a certain concentration must be exceeded in *all* patients at all times for consistent efficacy, but we recognize that this is an untested hypothesis. We cannot determine with confidence the thresh-

Table 3. Best Fit Two-Compartment Parameter Estimates (± SE)* with Adjustments for Effects of Cardiopulmonary Bypass (CPB) and Weight (wtkg)

$k_{10} = 0.014\ (\pm\ 0.002) - 0.005\ (\pm\ 0.001) \cdot I_{CPB}$
$k_{12} = 0.018\ (\pm\ 0.003)$
$k_{21} = 0.021\ (\pm\ 0.007)$
$V_1 = 0.149\ (\pm\ 0.012) \cdot wtkg - 1.61\ (\pm\ 0.41) \cdot I_{pre\text{-}CPB}$

Indicator covariates:

$$I_{CPB} = \begin{cases} 0: & \text{before and after CPB} \\ 1: & \text{during CPB} \end{cases}$$

$$I_{pre\text{-}CPB} = \begin{cases} 0: & \text{during and after CPB} \\ 1: & \text{before CPB} \end{cases}$$

* Tabulated values are population estimates, *i.e.*, estimates for a typical patient. The variance for interpatient variability (Ω) were estimated as 0.26, 0.0061, 0.38, and 0.042 · wtkg for k_{10}, k_{12}, k_{21}, and V_1, respectively. Units for k_{10}, k_{12}, and k_{21} are in min^{-1}; those for V_1 are in l.

Table 4. Pharmacokinetic Model Parameter Estimates (Mean ± SE)

	Before CPB	CPB	After CPB
k_{10}	0.014 ± 0.002	0.009 ± 0.002	0.014 ± 0.002
k_{12}	0.018 ± 0.003	Unchanged	Unchanged
k_{21}	0.021 ± 0.007	Unchanged	Unchanged
V_1 (l) at 80 kg	10.3 ± 0.8	11.9 ± 1.0	11.9 ± 1.0
V_1 (l) (weight adjusted)	0.149 l/kg* − 1.61 L	0.149 l/kg*	0.149 l/kg*
ξ	0.52 ± 0.06	Unchanged	Unchanged
V_2 (l) at 80 kg	8.5 ± 1.3	9.8 ± 1.7	9.8 ± 1.7
V_2 (l) (weight adjusted)	0.13 l/kg* − 1.4 L	0.13 l/kg*	0.13 l/kg*
Cl_1 (l/min) at 80 kg	0.15 ± 0.01	0.11 ± 0.02	0.17 ± 0.02
Cl_1 (l/min) (weight adjusted)	0.0021 l · kg^{-1} · min^{-1}* − 0.023 l/min	0.0013 l · kg^{-1} · min^{-1}* − 0.015 l/min	0.0021 l · kg^{-1} · min^{-1}*
Cl_2 (l/min) at 80 kg	0.18 ± 0.03	0.21 ± 0.03	0.21 ± 0.03
Cl_2 (l/min) (weight adjusted)	0.0027 l · kg^{-1} · min^{-1}* − 0.029 l/min	0.0027 l · kg^{-1} · min^{-1}*	0.0027 l · kg^{-1} · min^{-1}*

See Results for description of pharmacokinetic parameters.

Formula used: $V_2 = k_{12}/k_{21} \cdot V_1$; $Cl_1 = V_1 \cdot k_{10}$; $Cl_2 = V_1 \cdot k_{12}$

* The weight adjusted terms containing kg^{-1} as a unit need to be multiplied by the patient's weight in kg to calculate the parameter. For example an 80-kg patient, pre-CPB could have a V_1 (l) = 80 kg · 0.149 l · kg^{-1} − 1.61 l = 10.3 l.

SE = standard error; CPB = cardiopulmonary bypass.

old concentration for TA that would completely inhibit fibrinolysis, but it is likely to be less than 334 μM.[9,12] Based on our graphs of observed/predicted TA concentrations (fig. 2), we anticipate that our model prediction could overestimate the actual TA concentration by as much as 50%. Thus, we regard 334 μM as a conservative target (see recommendation 1, fig. 4) for the typical patient to minimize the likelihood of any patient having an unexpectedly low and potentially ineffective TA concentration. For high-risk bleeding patients we estimated the need to maintain the TA concentration above 800 μM, which corresponds with our current recommended dosing of TA 100 mg/kg as single bolus before surgery.

Discussion

Our study demonstrates that TA is rapidly eliminated by patients undergoing cardiac surgery with CPB when given as a single bolus dose. High-dose TA (50 mg/kg and 100 mg/kg) was associated with much higher peak plasma concentrations than low-dose TA (10 mg/kg + 1 mg · kg^{-1} · hr^{-1} × 10 h) and maintained longer steady concentration within theoretically assumed therapeutic range. Cardiopulmonary bypass increased the volume of distribution of the central compartment (V_1) by 1.61 and reduced the elimination rate constant (k_{10}).

A previous study[7] of TA pharmacokinetics in three healthy volunteers using a 3-compartment model reported parameter estimates similar to our study's pre-CPB values with their V_1s equal to 10.0, 9.0, and 8.9 l *versus* 8.2, 10.3, and 9.3 l, respectively, using our model after weight adjustments; k_{10} s of 0.012, 0.013, and 0.013 min^{-1} *versus* 0.014 for our model; k_{12} s of 0.026, 0.021, and 0.029 min^{-1} *versus* 0.018 min^{-1} for our model. We recognize that the common micro-rate constants from a 3-compartment model might vary from those based on a 2-compartment model. After our results were presented as an abstract,[14] Fiechtner *et al.*[15] reported TA concentrations in 19 patients undergoing CPB during cardiac surgery, some of whom had abnormal creatinine concentrations. No formal pharmacokinetic analysis was performed. Repeated measures analysis showed that patients with renal insufficiency had significantly higher TA concentrations post-CPB than patients with normal renal function. When we used our best model to simulate the Fiechtner *et al.* dosing regimen, we predicted TA concentrations that fell within the range of their observed concentrations in their patients. For example: their TA concentrations, mean (95% CL), after 5 min on CPB were 27.6 (23.8, 31.4) μg/ml *versus* our predicted concentration of 31.2 μg/ml; after 30 min on CPB, their concentrations were 31.4 (25.6, 37.2) *versus* our simulated concentration of 26.5 μg/ml; and after 60 min on CPB, their concentrations were 29.9 (23.8, 34.6) *versus* our simulated concentration of 24.0 μg/ml. The Fiechtner data independently support both our assay technique and our pharmacokinetic model.

Based on previous *in vitro* and *in vivo* studies, effective control of systemic fibrinolysis appears to require a plasma concentration of at least 64–95 μM. Andersson *et al.*[8] measured the fibrinolytic activity of tissue extracts in the presence of increasing concentrations of TA. A 98–100% reduction of the tissue activator activity required a concentration of 636 μM. An 80% inhibition required a concentration of 64 μM. Others have reported a plasma concentration of 30–65 μM as sufficient to inhibit fibrinolysis to an effective therapeutic degree.

No previous study has examined the pharmacokinetics of TA in patients undergoing cardiac surgery. We found that a 2-compartment model with adjustments for CPB performed well. Even though we had only a limited number[1–2] of samples during CPB, we were able to identify that CPB adjustment produced a statistically sig-

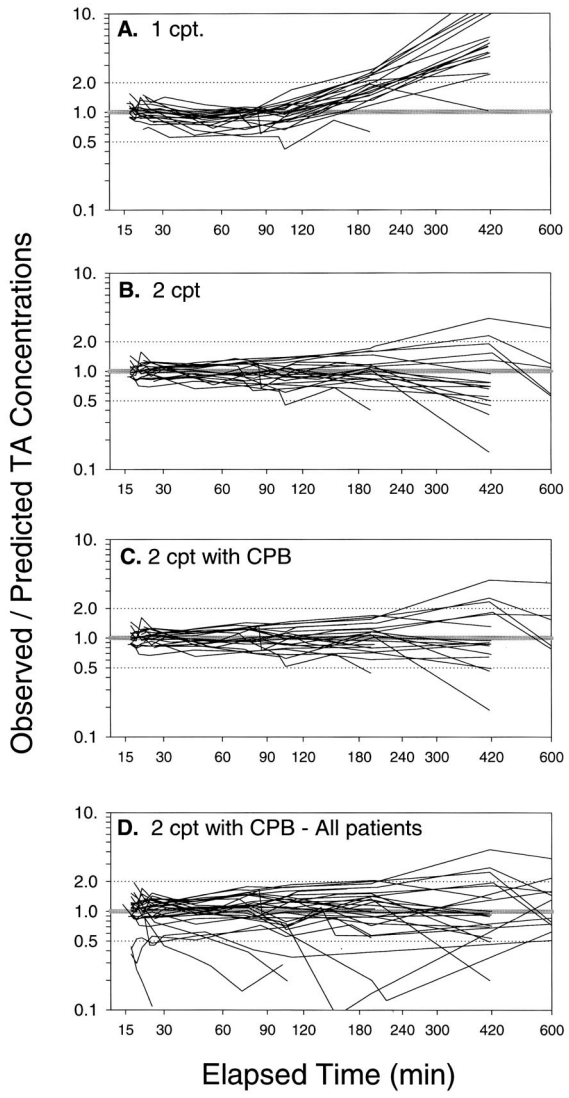

Fig. 2. The observed and predicted concentration of tranexamic acid (TA) in blood using different compartmental elimination models is shown. (*A*) Data from groups TA 50 and TA 100 are fit to a 1-compartment elimination model. Note that the model performs poorly at later times. (*B*) Data from groups TA 50 and TA 100 are fit to a simple 2-compartment model without adjustments for CPB. The model performs reasonably well, and later time points are distributed both above and below the line of identity, indicating a minimal bias. (*C*) Data from groups TA 50 and 100 were fit to a 2-compartmental model with CPB corrections as described in the text. Note that this resulted in some modest improvement in the fits, particularly at times earlier than 240 min. (*D*) Data from all three groups were fit to a CPB-corrected model. Note that inclusion of group TA 10 dramatically increases the variability. Nevertheless, the CPB-corrected model provided the best fit to the data, whether for all three groups or when the data from group TA 10 were excluded, as judged by both Schwarz-Bayesian Criterion and visual inspection of plots.

nificant improvement. Clearly, additional samples might have allowed us to better characterize the effects of CPB on TA kinetics.

We and other authors have tested for the effects of CPB on pharmacokinetics of other drugs.[10,11,16] The approach we used in this study with TA resembles that of previous studies, where CPB was variously associated with increases in central compartmental volumes, reductions in clearance, or both effects. We did not specifically test for an effect of hypothermia *per se* during CPB in this study. In other investigations, hypothermic CPB has been associated with greater effects on clearance (*e.g.*, rocuronium, remifentanil, alfentanil, and clevidipine) than normothermic CPB.[17–22]

The usual dose of TA in noncardiac surgery is 10–15 mg/kg body weight given intravenously 2 to 3 times daily starting immediately before[12,23,24] or after[5] surgery, or 1 to 1.5 g orally 3 to 4 times daily. In primary orthotopic liver transplantation TA infusion (40 mg $\cdot$ kg^{-1} $\cdot$ hr^{-1} to a maximum dose of 20 g) from induction until portal vein clamping significantly reduces intraoperative blood loss and perioperative blood, plasma, platelets, and cryoprecipitate requirements compared with placebo.[25] Published guidelines suggest that the dose of TA be reduced in patients with renal impairment.[5,8]

Doses reportedly used in cardiac surgery vary widely: from 10 mg/kg before CPB followed by an infusion of 1 mg $\cdot$ kg^{-1} $\cdot$ hr^{-1} for 12 h thereafter, to 100 mg/kg bolus over 20 min before CPB. Since a minimum therapeutic plasma concentration of TA has been defined (using limited data) as roughly 127 μM, it would seem reasonable that dosing techniques should achieve or exceed this level during and in the immediate postoperative period. Figure 3 illustrates dosing regimens that have been reported to be effective in reducing bleeding after cardiac surgery. Note that many of these dosing techniques typically do not maintain effective TA concentration throughout a cardiac operation. Horrow *et al.*[12] compares a series of loading doses and maintenance infusions of TA. It is notable that the lowest efficacious loading dose and maintenance infusion, in the study by Horrow *et al.*,[12] yielded concentrations at or above the therapeutic threshold during most of the perioperative period. Fiechtner *et al.* in a study recently published, also found that the Horrow *et al.* dose yielded declining TA concentrations intraoperatively.[15]

We have also provided three new dosing schemes for use during cardiac surgery with CPB. One scheme aims to maintain a concentration similar to the peak achieved by the dosing technique recommended by Horrow *et al.*[12]; the other aims to maintain a concentration comparable to the one we achieved using a single dose of 50 and 100 mg/kg. When we implemented single dose techniques in our institution, we found that long CPB times resulted in an increased risk of postoperative bleeding. In this current analysis, we assumed that by maintaining a constant concentration of TA during the surgery, and for some the (as yet poorly defined) period after surgery, we may reduce blood loss after prolonged CPB runs. TA appears to be a very safe medication and we are not aware that TA concentrations in the range we studied have been associated with any sort of adverse

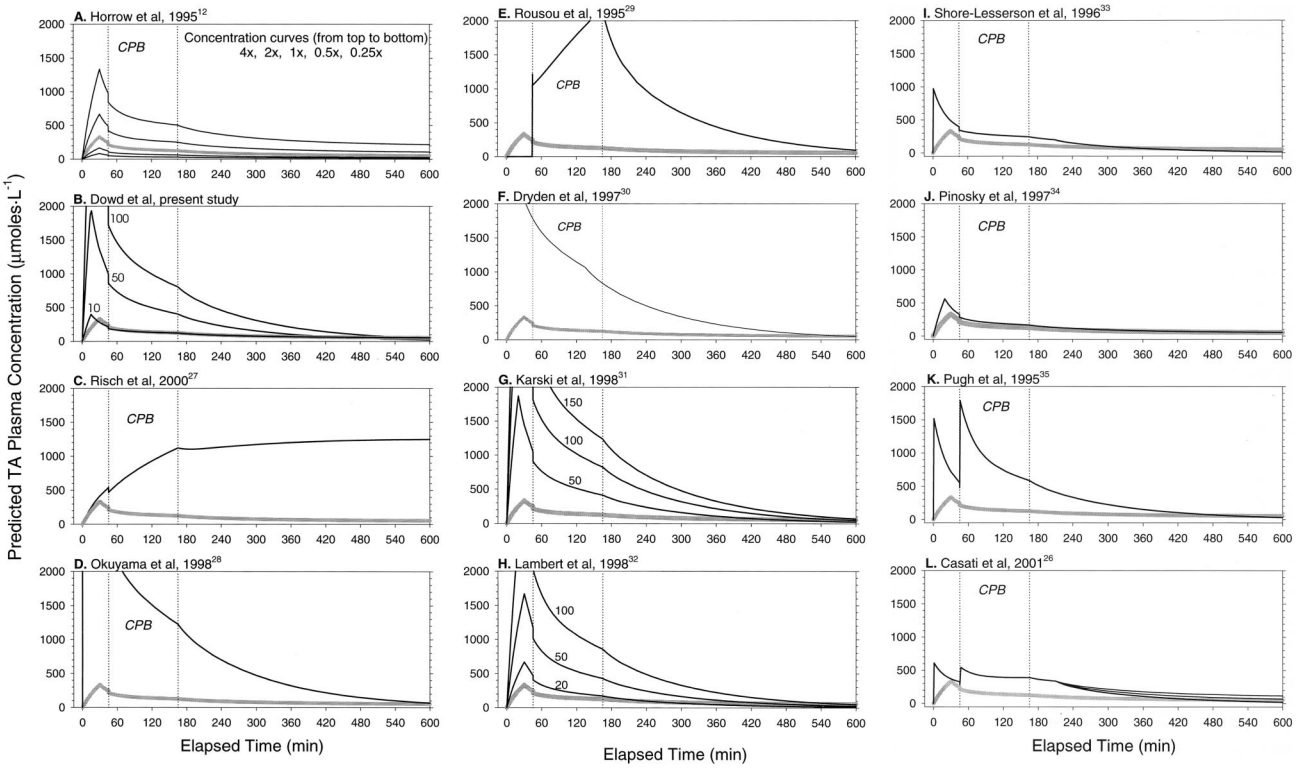

Fig. 3. Tranexamic acid (TA) concentration *versus* time plots simulated using our best CPB-adjusted pharmacokinetic model and dosing schemes. We assumed a patient weight of 80 kg and a 120 min duration of CPB. We assumed that 45 min of surgery would take place before and after CPB. The beginning and end of CPB are indicated by vertical dotted lines. (See Methods for details of simulations). On each plot we provide a simulation (gray line) for 10 mg/kg given over 30 min with a maintenance infusion of 1 mg · kg^{-1} · hr^{-1} (beginning at the end of the loading dose, and continuing for 12 h), the dose identified by Horrow *et al.*[12] as the minimum yielding efficacy. (*A*) Five dosing schemes described by Horrow *et al.* are shown. The one-time dose was described previously. All others are exact multiples or fractions of that dose. (*B*) The three dosing schemes used in the present study are shown. Note that the loading dose in all three groups was given over 15 rather than 30 min. This explains the difference between our group TA 10 and the one-time group of Horrow *et al.*[12]. (*C*) Risch *et al.*[27] infused 2 g/h for 10 h starting at the beginning of surgery. (*D*) Okuyama *et al.*[28] gave a single 160 mg/kg bolus (which we assumed would take 1 min to administer). (*E*) Rousou *et al.*[29] administered a 2 g bolus 1 min before CPB, with an 8 g bolus given by "slow infusion" during CPB. We have modeled the slow infusion as starting and ending with CPB. (*F*) Dryden *et al.*[30] gave a 10 g loading dose over 30 min concluding at the time of skin incision (our time 0). (*G*) Karski *et al.*[31] gave three loading doses (50, 100, and 150 mg/kg, as shown on the plot) over 20 min after induction of anesthesia. (*H*) Lambert *et al*.[32] gave three loading doses (20, 50, and 100 mg/kg, as shown on the plot) over 30 min starting after induction of anesthesia. (*I*) Shore-Lesserson *et al*.[33] administered a bolus of 20 mg/kg (we assumed that it was given over 1 min) at the start of surgery. A maintenance infusion of 1 mg/kg was given during surgery. (*J*) Pinosky *et al.*[34] administered a 15 mg/kg loading dose (we assumed that this took 20 min) at the start of surgery with a 1 mg · kg^{-1} · hr^{-1} maintenance infusion for 6 h. (*K*) Pugh *et al*.[35] gave a 2.5 g bolus (we assumed that it took 1 min) at the time of skin incision and added a 2.5 g dose to the CPB priming solution (we assumed mixing would take 2 min after initiation of CPB). (*L*) Casati *et al.*[26] gave all patients a 1 g bolus dose 20 min before sternotomy (we assumed that it took 1 min and began at time 0). All patients received a maintenance infusion of 400 mg/h throughout the operation. At the end of surgery, one group received 2 mg · kg^{-1} · hr^{-1} for 12 h, one group received 1 mg · kg^{-1} · hr^{-1} for 12 h, and one group received no additional TA after surgery. There is only limited agreement among investigators as to the amount and infusion rate of TA that is necessary to reduce bleeding during cardiac surgery.

events in patients undergoing cardiac surgery. Thus, our attempt to avoid excessive TA concentrations may not be necessary. Future studies should determine whether our suggested TA dosing scheme will render the drug safer or more efficacious at reducing perioperative red cell transfusions.

Casati *et al*. recently attempted to determine whether there is any benefit to administering TA after surgery.[26] We believe that this question remains unanswered, and in any case will likely depend on the intraoperative dosing technique used. Note in figure 3 that the three dosing schemes used by Casati *et al*. resulted in very similar TA concentrations in the postoperative period, and that only after several hours had passed did these concentrations differ among the groups by as much as 10%. This illustrates the value of using pharmacokinetic studies to guide experimental design. From not knowing the pharmacokinetic characteristics of TA in cardiac surgery patients, Casati *et al*. performed a rigorous (and likely very expensive) clinical trial, which because of the high TA blood concentrations achieved during and after surgery, would be unable to detect a disadvantage to allowing TA concentrations to fall below, say, 200 μM after completion of surgery. Had TA concentrations been

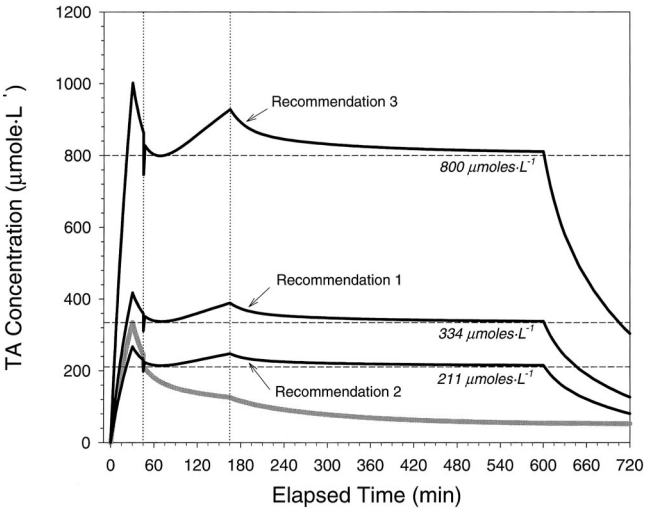

Fig. 4. A comparison between our recommended dosing schemes and that of Horrow *et al.*[12] For modeling purposes, we have assumed three alternatives; recommendation 1: that the peak concentration achieved by the one-time dosing scheme of Horrow *et al.*[12] should be the target concentration to be maintained as long as a TA effect is desired; in recommendation 2 we have attempted to maintain the concentration that would have been present at the start of CPB using the Horrow *et al.*[12] technique; in recommendation 3 we attempt to maintain the peak concentration achieved after a single 100 g/kg dose. We have also assumed a weight of 80 kg, 45 min of surgery before and after 120 min of CPB, and that there is no renal or hepatic failure. For recommendation 1, we suggest a 30 min loading dose of 12.5 mg/kg, a maintenance infusion of 6.5 mg · kg^{-1} · hr^{-1} starting immediately after the loading dose (and continued for 4 h after surgery), and an additional dose of 1 mg/kg to be added to the CPB priming solution. For recommendation 2, we suggest a loading dose of 8 mg/kg given over 30 min, a maintenance infusion of 4 mg · kg^{-1} · hr^{-1}, and 0.6 mg/kg in the CPB priming solution. For recommendation 3, to achieve and maintain TA concentration at 88 μM, we suggest a loading dose of 30 mg/kg plus 2 mg/kg added to the pump prime followed by 16 mg · kg^{-1} · h^{-1} continuous infusion.

maintained at lower values during and after CPB, the trial might have had power to detect whether postoperative TA dosing is needed.

In conclusion, adult cardiac surgery patients rapidly eliminate TA. During CPB, V_1 increases and k_{10} decreases, corresponding to an increase in central compartmental volume and a decline in TA elimination from the central compartment. If the practitioner would like to maintain the peak concentrations produced by Horrow's "one time" dosing scheme, we suggest that a loading dose of 12.5 mg/kg (or greater) given over 30 min, a maintenance infusion of 6.5 mg · kg^{-1} · hr^{-1} (or greater), and CPB priming dose of 1 mg/kg (or greater) to maintain TA concentration in blood greater than 345 μM in the typical adult patient undergoing cardiac surgery with CPB. If a higher blood concentration is sought, the loading dose of 30 mg/kg plus additional 2 mg/kg added to the pump prime followed by 16 mg · kg^{-1} · h^{-1} infusion will maintain TA concentration at 800 μM.

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Appendix

Reagents

HPLC-grade acetonitrile was purchased from Sigma-Aldrich (Milwaukee, WI). HPLC-grade methanol was supplied by Burdick & Jackson (Muskegon, MI). Protein sequencing-grade phenyl isothiocyanate (PITC) and L-norleucine were purchased from Sigma Chemical Co. (St. Louis, MO). HPLC-grade sodium acetate and sodium phosphate were purchased from J.T. Baker (Phillipsburg, NJ). Deionized distilled water was produced using a Barnstead (Dubuque, IA) purifying system. TA (for internal standards) was purchased from Pharmacia AB (Stockholm, Sweden).

Ultrafiltration

100 μl plasma was diluted with 100 μl 250 mM L-norleucine (Sigma, St. Louis, MO; N-8513) in 0.1 N HCl. Diluted plasma was transferred to Ultrafree-MC, 10,000 NMWL (Millipore, UFC3LGC, Bedford, MA) and centrifuged at 6,400 rpm for 60 min.

Derivatization

Each 50 μl filtrate was then taken to a small glass tube (Fisher, Springfield, NJ; 14–923A) and dried under vacuum (Aes 1010, Savant Instruments Inc., Holbrook, NY) for 60 min. Dry samples were then treated with 10 μl of a mixture of methanol-1 M NaAcetate-TEA (2:2:1, v/v). Samples were dried with a Speed Vac (Savant Instruments Inc., Holbrook, NY) for 40 min. Fresh derivatization reagents, namely methanol-TEA-water-PITC (7:1:1:1, v/v), were added in 20 μl to each sample and reacted for 20 min at room temperature. Samples were dried with a Speed Vac for 90 min. Derivatives were reconstituted in 100 μl of 5 mM $NaHPO_4$, pH 7.4-acetonitrile (950:50). Reconstituents were transferred to clear glass conical insert tubes.

High-performance Liquid Chromatography (HPLC)

The chromatographic system consisted of a 600 controller, an in-line degasser, a 717 plus autosampler, and a 996 photodiode array detector from Waters (Milford, MA). The analytical column was a NovaPak C_{18} (Waters, WAT086344) 3.9 $\times$ 300 mm, 4 μm, 60Å. The mobile phase A was 70 mM NaAcetate, pH 6.5-acetonitrile. 975:25 The mobile phase B was acetonitrile-methanol-water. 450:150:400 The eluent was delivered at a flow rate of 1 ml/min. The column temperature was maintained at 38°C. TA was monitored at 254 nm.

Assay Performance

Our assay technique provided linear standard curves over the range from 95 μM (15 μg/ml) to 12.5 mm (1962 μg/ml). Typically R^2 for linear regressions to standard curve was 0.98. The lowest concentration we have attempted to assay was 39 μM (6.2 μg/ml); the highest concentration we have tested was 4.7 mM (735 μg/ml). Standard deviations increased proportionate with measurements, permitting us to report a mean 6.4% coefficient of variation for day-to-day variation in our assay procedure.