Gender Does Not Influence Epsilon-Aminocaproic Acid Concentrations in Adults Undergoing Cardiopulmonary Bypass

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Epsilon-aminocaproic acid (ϵ-ACA) is administered to cardiac surgery patients to reduce blood transfusions. Highly water-soluble drugs, such as ϵ-ACA, often have larger distribution volumes in males than in females. We hypothesized that ϵ-ACA concentrations using this dosing scheme would differ by gender because of differences in body composition and weight-adjusted volumes of distribution. Ten men and 10 women undergoing elective coronary artery surgery with cardiopulmonary bypass (CPB) received a 50 mg/kg ϵ-ACA initial dose over 20 min and a 25 $mg \cdot kg^{-1} \cdot h^{-1}$ ϵ-ACA maintenance infusion for 4 h. The area under the ϵ-ACA arterial concentration versus time curves was compared by using analysis of variance. Measured ϵ-ACA concentrations were smaller than predicted by the published model, but the area under the concentration versus time curves was not significantly different between men and women. Combining the present concentration data with that previously published, our updated two-compartment model included the following estimated population pharmacokinetic values: V_1 (11.8 L pre-CPB, 14.9 L during and after CPB), V_2 (12.0 L pre-CPB, 15.0 L during and after CPB), Cl_1 (0.125 L/min pre-CPB, 0.037 L/min during CPB, 0.156 L/min after CPB), Cl_2 (0.155 L/min pre-CPB, 0.013 L/min during CPB, 0.193 L/min after CPB).

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Epsilon-aminocaproic acid (ϵ-ACA) is given to patients having surgery with cardiopulmonary bypass (CPB) to reduce mediastinal shed blood and the need for blood transfusions (1). ϵ-ACA was widely adopted into cardiac anesthesia practice without a detailed knowledge of its pharmacokinetics or pharmacodynamics in cardiac surgery patients. We proposed an ϵ-ACA dosing scheme based on pharmacokinetic modeling in surgery patients that was designed to maintain ϵ-ACA concentrations at 260 mg/L (roughly twice the concentration that inhibits fibrinolysis *in vitro*) (2). Highly water-soluble drugs may have larger distribution volumes in males than in females, presumably because of gender differences in the relationships between extracellular fluid stores and weight (3–6). Weight-adjusted dosing will not account for differences in body composition; thus, the relationship between weight and distribution volumes could vary by gender. Based on ϵ-ACA's water solubility and relative small central distribution volume, we hypothesized that ϵ-ACA concentrations would be smaller in men than women due to differences in weight-adjusted volumes of distribution (7). Therefore, we tested for effects of gender on ϵ-ACA blood concentrations in a series of male and female patients undergoing elective cardiac surgery.

Methods

Consenting patients (10 men and 10 women) undergoing elective cardiac surgery with mild to moderate hypothermic CPB were studied. Our IRB reviewed and approved our study. After receiving heparin, all patients received IV ϵ-ACA: a 50 mg/kg initial dose over 20 min and a 25 $mg \cdot kg^{-1} \cdot h^{-1}$ maintenance infusion for 4 h. Previous simulations using our published pharmacokinetic scheme suggested that this dosing regimen would maintain ϵ-ACA concentrations at roughly 260 mg/L. All but one patient received the initial dose using an infusion pump. One patient, through a misunderstanding between the clinical and research teams, received the initial dose as a rapid bolus injection. All patients received the maintenance infusion using an infusion pump.

Fourteen arterial blood samples were to be collected at defined times (see Table 1). Additional samples were

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sometimes available for analysis when small volumes (1–2 mL) of blood procured for intraoperative measurements remained unused after activated clotting time and arterial blood gas analyses had been performed. Thus, a varying number of samples was actually collected in each patient because of concurrent sample times (e.g., the "10 min after completion of initial dose" and the "2 min after initiation of CPB" collections sometimes coincided), or because of patient-related issues (concerns about intraoperative bleeding in one patient led the clinical team to request that ϵ-ACA be infused beyond the 4-h maximum as specified in our protocol, preventing our obtaining "washout" samples). All blood samples were analyzed by using high-performance liquid chromatography as described previously (2). Standard curves for the assays were linear over the range of concentrations studied in this analysis. We observed nearly constant coefficients of variations for our assay (at 312.5 μg/mL, $n = 37$, coefficient of variation = 5%; at 156.3 μg/mL, $n = 36$, coefficient of variation = 7%; at 78.1 μg/mL, $n = 23$, coefficient of variation = 4%; at 39.1 μg/mL, $n = 18$, coefficient of variation = 5%) except at very small concentrations where our results showed greater variation (at 19.5 μg/mL, $n = 15$, coefficient of variation = 22%).

The effect of gender on ϵ-ACA concentrations was tested by using analysis of variance (ANOVA) of the areas under the concentration versus time curves (AUCs) through the 240-min measurement. A power analysis was performed to determine the sample size necessary to detect a 50% arithmetic scale difference in AUC between males and females, assuming a coefficient of variation equal to 50% and a gender effect size of 50%. On the log scale, this would translate to a standard deviation of approximately 0.5 and an effect size of 0.69. Based on these estimates, a sample size of 10 per gender group should give 84% power.

AUC was calculated by the trapezoidal method. The ANOVA used weighted least squares (the weighting factor was variance by gender). The duration of CPB was included in the model as a covariate to account for the reduced elimination of ϵ-ACA that we had previously shown to occur during CPB (2). We also adjusted the ANOVA for heteroscedasticity by using weighted least squares. An examination of the residual values of the AUC ANOVA demonstrated that logarithmic transformation was appropriate to "normalize" the AUC data. This was confirmed by Shapiro-Wilks tests showing significant deviations ($P < 0.03$) from normality when the data were not log-transformed. Goodness of fit of our present data to our published model (2) was determined by using a plot of observed/predicted concentrations.

Finally, concentration versus time data from our previous (2) and from the present study were combined to develop an updated model to predict ϵ-ACA pharmacokinetics. Concentration versus time data were fit to compartmental models by using the nonlinear mixed-effects regression techniques of the NONMEM (Version V, 1.1) software package (NONMEM Project Group, University of California, San Francisco, CA). Models were fit both with and without covariate adjustments for variables including age, weight, height, body mass index (BMI) (weight/height) (2), creatinine, and creatinine clearance. The latter was estimated by using the equation proposed by Cockcroft and Gault (7). We tested models that included compartmental model variables as linear and exponential functions of covariates. In addition, time-dependent covariates indicating before, during, and after CPB were tested for inclusion into the pharmacokinetic model as described previously (2). Model rate constants, k_{10}, k_{12}, k_{21}, k_{20}, etc., and the central compartment's volume of distribution, V_1, were estimated directly by the NONMEM program. Variable 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 micro-rate constant describing drug movement from compartment 1 to compartment 2). Clearances (L/min) and V_2 were calculated by using standard formulae. The model variables for the random interpatient variability of the rate constants and V_1 were assumed to be lognormal in distribution. We tested additives, constant coefficient of variation, combined additive and constant coefficient of variation, and power function residual error models (8).

The selection of the best model fit was based on its satisfying all of the following: 1) the ability of NONMEM to estimate the standard errors of all variables, 2) the 95% confidence intervals for each estimated structural variable of the model indicated significance (i.e., the confidence intervals did not include 0 if additive or 1 if multiplicative), and 3) of all the models satisfying the above two criteria, the one having the largest (most positive) Swartz-Bayesian Criterion was considered the best model.

Table 1. Protocol Blood Sample Times

5 min after completion of the ϵ-ACA initial dose
10 min after completion of the ϵ-ACA initial dose
30 min after completion of the ϵ-ACA initial dose
60 min after completion of the ϵ-ACA initial dose
120 min after completion of the ϵ-ACA initial dose
180 min after completion of the ϵ-ACA initial dose
240 min after completion of the ϵ-ACA initial dose
Immediately before initiation of CPB
2 min after initiation of CPB
Immediately before discontinuation of CPB
2 min after discontinuation of CPB
Immediately before discontinuation of the ϵ-ACA infusion
10 min after discontinuation of the ϵ-ACA infusion
30 min after discontinuation of the ϵ-ACA infusion

ϵ-ACA = epsilon-aminocaproic acid, CPB = cardiopulmonary bypass.

Because compartmental pharmacokinetic models are mathematically exponential in form, we measured model performance on the log-scale using the geometric performance error (GPE). As a simple measure of overall model performance, we used the 50th, 75th, and 95th percentiles of the GPE over all samples. The GPE for each sample is equal to antilog (|log (observed) − log (predicted)|). Additional details about pharmacokinetic modeling procedures are given in the Appendix.

All statistical analyses were accomplished by using SAS Version 8.0 (SAS Institute, Cary, NC). $P \leq 0.05$ was considered significant.

Results

Mean ages and weights (mean ± SD) were 63 ± 10 and 68 ± 8 yr, and 87 ± 9 and 71 ± 17 kg, respectively, for men and women. Other demographic and surgical data pertaining to these patients are provided in Table 2. Note that the differences in estimated creatinine clearance between males and females approached statistical significance.

The CPB circuits were primed with a combination of crystalloid (mean 1325 mL, median 1375 mL in males and mean 1285 mL, median 1375 mL in females) and colloid solutions (all circuits were primed with 250 mL of 5% albumin and one female patient also had 1 U of packed red blood cells included in the priming volume). Aspartate and glutamate enriched blood cardioplegia was used in all cases (mean volume 2355 mL, median 1950 mL for males and mean volume 2865 mL, median 2500 mL for females). All patients were cooled during CPB (mean lowest bladder temperature 30.8°C, median 32°C for males and mean 30.6°C, median 30.7°C for females). Urine output during CPB was similar in males (mean 550 mL, median 500 mL) and females (mean 575 mL, median 360 mL). One female patient was the only one to undergo hemoconcentration during CPB. Additional crystalloid administered during CPB (not including cardioplegia solutions) was similar in males (mean 365 mL, median 125 mL) and females (mean 570 mL, median 250 mL). The volume of colloid (including packed red cell units, but not including washed shed blood) administered during CPB was similar for males (mean 238 mL, median 0 mL) and females (mean 325 mL, median 375 mL).

At all times during surgery, measured ε-ACA concentrations tended to be >130 mg/L, but less than predicted using the published pharmacokinetic model (Figs. 1 and 2) (2). Note that there is no evidence for an effect of gender on ε-ACA concentrations in Figure 1 or Figure 2. Although most concentrations exceeded 130 mg/L, the typical concentration was not 260 mg/L, which had been our target (2). A comparison of AUC values by ANOVA showed no significant difference between males and females (Fig. 3). The least squares geometric means difference between males and females expressed as the ratio of male AUC/female AUC (95% confidence limits) was 1.09 (0.80, 1.47). We also compared AUC over the time intervals from 30–60 min, 60–150 min, and 150–240 min, and again there were no significant differences by gender.

Given the consistent overestimation of ε-ACA concentrations using the published pharmacokinetic model (Fig. 2), we surmised that the published ε-ACA pharmacokinetic model could be improved. We combined the data from the patients ($n = 22$) in our previous study with the data in the present study to produce an updated model for ε-ACA elimination kinetics. The criteria by which we selected the best model are provided in Table 3. The model variables are provided in Table 4. Our model that best fit the data had the same model structure as our previously reported pharmacokinetic model (2). The model structure is summarized in the Appendix. A plot of observed versus predicted concentrations using the combined data and the updated pharmacokinetic model is provided in Figure 4. By using the updated model, we predict that an initial dose of 70 mg/kg given over 20 min and a maintenance infusion dose of $30\ \text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ will maintain ε-ACA concentrations at approximately 260 mg/L so that <5% of patients will have subtherapeutic (<130 mg/L) ε-ACA concentrations during drug infusion (Fig. 5).

Discussion

We found no significant differences between males and females in overall ε-ACA concentrations, by using an analysis of AUC. Highly water-soluble drugs such ε-ACA often have larger distribution volumes in males than females (3–6). These differences are sometimes eliminated by weight-adjusted dosing. We note that BMIs of males and females were not significantly different in the older patients that we studied. Premenopausal females typically have BMIs that differ from those of similarly aged males, reflecting differences in relative amounts of muscle and fat. Thus, our data do not permit us to exclude a possible gender difference in ε-ACA pharmacokinetics in younger patients.

We have previously observed that patients with renal failure show markedly delayed ε-ACA elimination (2). Our female subjects had reduced serum creatinine concentrations and reduced estimated creatinine clearances compared with our male subjects, but only the former difference was statistically significant. Reduced creatinine clearance should have exaggerated any difference in ε-ACA concentrations produced by gender-based differences in

Table 2. Demographic Characteristics of the Patients

	Males	Females	*P* values
Number of patients	10	10	
Age (yr)	63 ± 11	68 ± 8	0.30
Height (cm)	178 ± 3	162 ± 5	<0.0001
Weight (kg)	87 ± 9	70 ± 9	0.02
Body surface area (m^2)	2.1 ± 0.1	1.8 ± 0.2	0.002
Body mass index (kg/m^2)	27 ± 3	27 ± 6	0.83
Preoperative creatinine (mg/dL)	0.9 ± 0.2	0.8 ± 0.2	0.04
Preoperative estimated creatinine clearance (mL/min)	105 ± 33	78 ± 28	0.07
Duration of cardiopulmonary bypass (min)	118 ± 42	145 ± 37	0.13
Coronary artery bypass grafting	9	7	
Valve surgery	1	1	
Combined coronary + valve surgery	0	2	

Data are mean ± SD or incidence (*n*) Student's *t*-test was used for statistical comparisons. Creatinine clearance was estimated by using the Cockcroft-Gault equation (7).

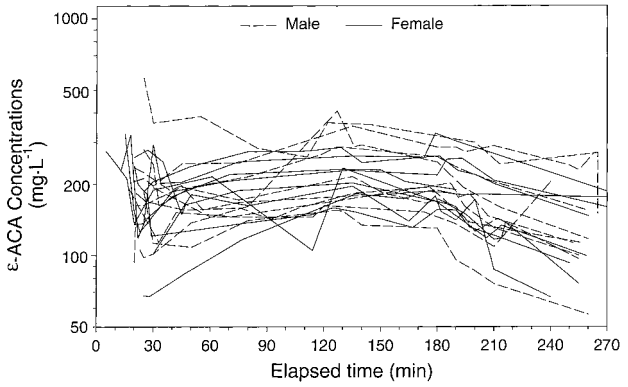

Figure 1. Measured concentrations of epsilon-aminocaproic acid (ϵ-ACA) after a 50 mg/kg initial infusion over 20 min and a 25 $mg \cdot kg^{-1} \cdot h^{-1}$ maintenance infusion for 4 h. Elapsed time is measured from initiation of the bolus dose.

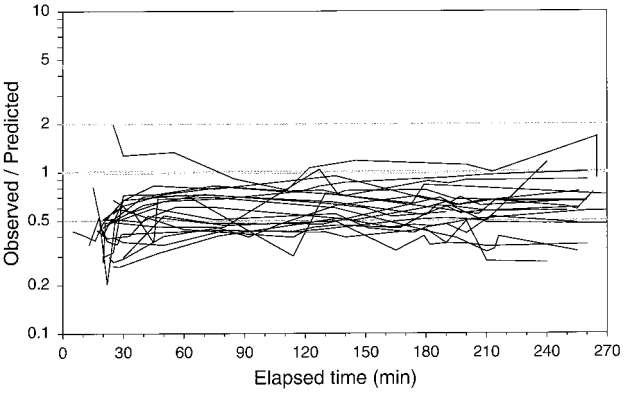

Figure 2. Observed/predicted concentrations of present ϵ-aminocaproic acid data using the pharmacokinetic model described in Ref. 2. All patients received a 50 mg/kg initial dose over 20 min and a 25 $mg \cdot kg^{-1} \cdot h^{-1}$ maintenance infusion for 4 h. Elapsed time is measured from the initiation of the bolus dose.

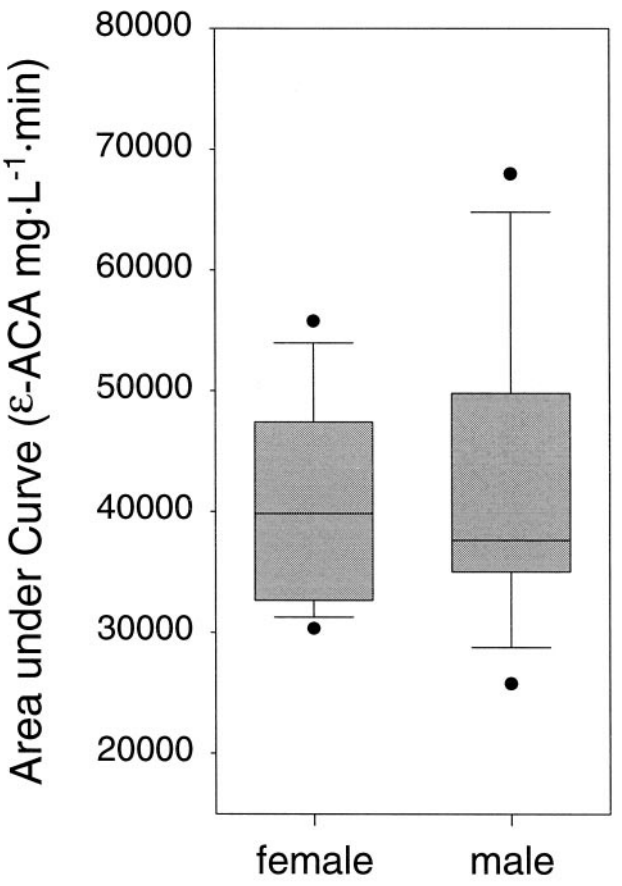

Figure 3. Box plot of area under the concentration versus time curves (AUCs) for males and females. The box contains the 25th to 75th percentiles. The median value is denoted by a line within the box. The "whiskers" include the 90th percentile values and the dots above and below the bars represent the maximal and minimal values. The least squares geometric mean ratio of male AUC/female AUC (95% confidence limits) was 1.09 (0.80, 1.47), and this was not significant. ϵ-ACA = epsilon-aminocaproic acid.

V_1. Nevertheless, we observed no gender-based differences in ϵ-ACA concentrations. It is tempting to speculate whether gender differences in renal function might lend to gender differences in toxic effects from ϵ-ACA. Nevertheless, we observed no gender difference in ϵ-ACA concentrations, and our study was underpowered to study acute renal failure. In a recently reported retrospective study, no association

Table 3. Model Selection Criteria for Selected Model Fits to Updated Data Set[a]

	Objective function	SBC	GPE_{50}	GPE_{75}	GPE_{95}
1 compartment (weight)	111,827	−5932	1.3	2.0	2.5
1 compartment (weight, CPB [V_1, k_{10}])	111,786	−5918	1.3	1.6	2.6
2 compartment (weight)	111,480	−5771	1.3	1.5	2.3
2 compartment (weight, CPB [V_1])	11,468	−5768	1.3	1.5	2.3
2 compartment (weight, CPB [V_1, k_{10}])	11,307	−5691	1.3	1.6	2.3

Objective function: smaller is better fit; SBC = Schwarz-Bayesian criterion: larger is better fit; GPE_{50} = 50th percentile of geometric performance error, GPE_{75} = 75th percentile of geometric performance error, GPE_{95} = 95th percentile of geometric performance error, CPB = Cardiopulmonary bypass.
See text for description of GPEs.
[a] Updated data set includes concentration versus time data from present study as well as patients in Ref. 2.

Table 4. Variable Estimates (±SE) from Our Best Model Using Updated[a] Data Set

Variables	Pre-CPB	CPB	Post-CPB
k_{10} (min^{-1})	0.0105 ± 0.0008	0.0025 ± 0.0018	0.0105 ± 0.0008
k_{12} (min^{-1})	0.0130 ± 0.0021	0.0130 ± 0.0021	0.0130 ± 0.0021
k_{21} (min^{-1})	0.0129 ± 0.0018	0.0129 ± 0.0018	0.0129 ± 0.0018
V_1 (L)[b]	11.8 ± 1.7	14.9 ± 0.2	14.9 ± 0.2
Derived variables			
Cl_1 (L/min^{-1})	0.125 ± 0.020	0.037 ± 0.027	0.156 ± 0.019
Cl_2 (L/min^{-1})	0.155 ± 0.033	0.013 ± 0.002	0.193 ± 0.037
V_2 (L)[b]	12.0 ± 2.1	15.0 ± 2.1	15.0 ± 2.1

SE = standard error.
[a] Updated data set includes concentration versus time data from the present study as well as that in Ref. 2.
[b] Assuming 80-kg weight.

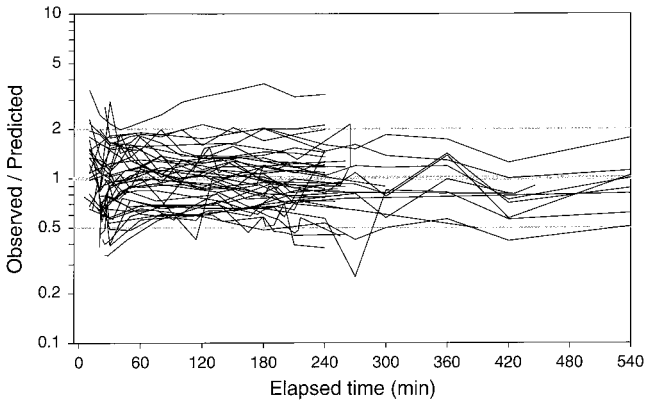

Figure 4. Observed/predicted concentrations of ϵ-aminocaproic acid using both previous (n = 22) and present (n = 20) data sets. These data were combined to generate an updated two-compartment model with cardiopulmonary bypass adjustments for V_1 and k_{10}. This model had a similar form to that presented in Ref. 2, and its variables are provided in Table 4. Elapsed time is measured from the beginning of the initial dose.

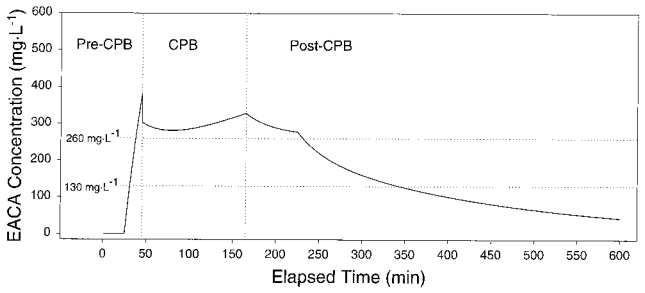

Figure 5. Predicted epsilon-aminocaproic acid (ϵ-ACA) concentrations after an initial dose of 70 mg/kg given over 20 min (ending with initiation of cardiopulmonary bypass) and maintenance infusion of 30 mg/kg given for 3 h thereafter. The patient's weight was assumed to be 80 kg, and the duration of cardiopulmonary bypass was 120 min.

was found between ϵ-ACA and postoperative renal dysfunction (9).

There are a few possible methods by which we could have tested for an effect of gender on ϵ-ACA elimination. We chose to compare AUCs between men and women, because this technique would not require us to assign the influence of gender to any particular pharmacokinetic variable, and would allow us to make few compartmental assumptions about ϵ-ACA elimination. However, the overall shapes of the concentration-time curves could have differed between males and females without a significant difference in the AUCs. A graphic examination of Figure 1 does not suggest any overall differences in the shapes of the concentration versus time curves and the intermixing of the male and female curves further suggests no gender effects. In any case, we found no evidence for any influence of gender on ϵ-ACA AUCs in this group of older adults undergoing coronary artery surgery.

Although gender influences on pharmacokinetics and pharmacodynamics of drugs have long been recognized in experimental animals (10), pharmacokinetic models usually do not account for gender differences. Gender-based differences have been reported in the rate of Phase I metabolic reactions including CYP1A2, CYP2C19, CYP2D6, CYP2E1, and CYP3A4

(all members of the cytochrome P450 superfamily) (3,11,12). Nevertheless, the specific metabolic pathways relevant to ε-ACA elimination are unknown, and may not have gender differences.

Although studies of many pharmacologically active compounds have shown gender differences in peak blood concentrations, few drugs demonstrate true gender differences in pharmacokinetic variables after differences in lean body mass have been eliminated. For example, with albuterol, females had significantly smaller volumes of distribution than males unless an adjustment for ideal body weight was applied (13). After the adjustment, there was no significant difference between the sexes in albuterol pharmacokinetics. There is an occasional drug with significant gender differences in pharmacokinetics. Some drugs recently recognized to have such differences include verapamil (14), tenidap (15), tirilazad (16), modafinil (17), fluvoxamine (18), and vecuronium (19).

In our previous study, and in our combined data, a two-compartment model with CPB adjustments proved best. Differences between our present patients and those reported in our previous study were minimal, but pertinent. All of the patients in the previous study had a single attending surgeon; the patients in the present study had five different attending surgeons. This likely increased variation in our measurements because of minor differences in surgical and CPB techniques. More than half of the patients in the previous study received ε-ACA only after CPB, and these patients had better fits to pharmacokinetic models than did the patients who received ε-ACA before, during, and after CPB. All of the patients in the present study received ε-ACA before, during, and after CPB. The *a priori* expectation would be that the present patients would demonstrate greater variation than the previous patients would. This, in fact, seemed to be the case. We observed some small, but important, differences in our updated model as compared with the previously published one (2), the most notable of which was that we observed a larger V_1 in our updated model.

There is no evidence that strict adherence to an ε-ACA dosing scheme that maintains stable ε-ACA blood concentrations either improves efficacy or reduces ε-ACA-related complications. Nevertheless, we suspect that any ε-ACA-related thrombotic complications will occur more frequently when excessive ε-ACA concentrations are present. Likewise, there is no point in deliberately exposing patients to drug concentrations below those that are effective. Studies of ε-ACA efficacy were conducted before detailed knowledge of its pharmacokinetics in cardiac surgery patients was available (20). It should be possible to administer ε-ACA in a precise way so that the minimal concentrations associated with efficacy, perhaps using a secondary marker (e.g., reduced detection of fibrin degradation products), can be determined.

Our study has inevitable limitations. First, there is some small error associated with our assay technique and there is always the possibility of mislabeled or mistimed samples. We anticipated being powered to detect only a fairly large difference in AUC between men and women. We studied the patients who usually receive the drug, and these patients often undergo CPB. We knew from our previous pharmacokinetic modeling that we would need to include several CPB-related adjustments to the usual variables that would be fit for a two-compartment elimination model. Thus, we knew that we would not likely be able to resolve additional indicator variables for gender (which would have increased the number of fit variables beyond the capabilities of the NONMEM program and this data set while using a multicompartmental model). The variable durations of CPB in our patients led to additional variations in the time during which drug clearance was reduced. The variable duration of CPB and variable timing of sampling led to differences in plasma sampling times and numbers among the patients, and could have resulted in bias either for or against our ability to detect a small gender difference in AUC. It is probably not possible to achieve true "steady-state" conditions during CPB, and, ideally, "steady-state" should be present to reduce errors during pharmacokinetic modeling. Although none of these patients suffered a severe coagulopathy, blood loss and fluid replacement varied from patient to patient and this could have led to additional variations in ε-ACA blood concentrations. All of these confounding effects tended to reduce our ability to detect differences between males and females.

It is common pharmacokinetic practice to assess the utility of a drug elimination model by comparing the observed to the predicted drug concentrations while using the very drug concentrations that were used to develop the elimination model. The potential pitfalls of this approach are illustrated in this study. By using our previously reported model and a drug dosing technique based on that model, we discovered that we consistently obtained drug concentrations smaller than predicted. Therefore, not knowing which set of patients would best predict ε-ACA elimination in future patients, we have developed a new model that incorporated the data from all of our adult study patients. It remains for other investigators to determine how well our updated model accomplishes its goals.

In conclusion, we found no evidence for a gender-based difference in ε-ACA pharmacokinetics. By using a recommended initial dose of 70 mg/kg and a 30 $mg \cdot kg^{-1} \cdot h^{-1}$ maintenance infusion, we would expect that the typical patient would maintain ε-ACA blood concentrations in the 260 mg/L range throughout CPB and recovery (Fig. 5). Moreover, by using this regimen, almost no patient would have ε-ACA concentrations below the 130 mg/L concentration associated with inhibition of fibrinolysis *in vitro*.

Appendix

Structural Model:

$k_{10} = \theta_1 + \theta_5 \cdot I_{CPB}$

$k_{12} = \theta_2$

$k_{21} = \theta_3$

$V_1 = \theta_4 \cdot wtkg + \theta_6 \cdot I_{PreCPB}$

where: θ_1 thru θ_7 are population parameters estimated by NONMEM

I_{CPB} = 0: during pre- and post-CPB
1: during CPB

I_{PreCPB} = 0: during and post-CPB
1: during and pre-CPB

Variance Model:

Interpatient variability

$\theta_{ij} = \theta_i \cdot e^{nij}$

where: θ_i = population parameters θ_1 thru θ_4

0_{ij} = individual patient estimates of θ_1 thru θ_4

η_{ij} = random variable normally distributed with mean 0 that accounts for the interpatient variability of θ_i associated with patient j

η_i = standard deviation of η_{ij} over all j for θ_i

Residual error

$Y = F + F^{\theta 7} \cdot \epsilon_{j,k}$

where: Y = the observed concentration

F = the predicted concentration

θ_7 = the power term estimated by NONMENM

$\epsilon_{j,k}$ = the residual error for observation k of patient j

σ = standard deviation of $\epsilon_{j,k}$ over all j,k

Parameter Estimates of Our Best Model

Parameter	Estimate ± standard error
θ_1	$0.011 \pm 0.0005\ min^{-1}$
θ_2	$0.018 \pm 0.002\ min^{-1}$
θ_3	$0.013 \pm 0.002\ min^{-1}$
θ_4	$0.19 \pm 0.02\ L \cdot kg^{-1}$
θ_5	$-0.008 \pm 0.001\ min^{-1}$
θ_6	$-3.0 \pm 0.7\ L$
θ_7	0.92 ± 0.008

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