Anesthesiology
1999; 90:1624–35

Pharmacokinetics of ϵ-aminocaproic Acid in Patients Undergoing Aortocoronary Bypass Surgery

John Butterworth, M.D., Robert L. James, M.S.,† Yonggu Lin, M.S.,‡ Richard C. Prielipp, M.D.,§ Allen S. Hudspeth, M.D.‖*

Background: **ϵ-Aminocaproic acid (EACA) is commonly infused during cardiac surgery using empiric dosing schemes. The authors developed a pharmacokinetic model for EACA elimination in surgical patients, tested whether adjustments for cardiopulmonary bypass (CPB) would improve the model, and then used the model to develop an EACA dosing schedule that would yield nearly constant EACA blood concentrations.**

Methods: **Consenting patients undergoing elective coronary artery surgery received one of two loading doses of EACA, 30 mg/kg (group I, n = 7) or 100 mg/kg (group II, n = 6) after CPB, or (group III) a 100 mg/kg loading dose before CPB and a 10 mg · kg^{-1} · h^{-1} maintenance infusion continued for 4 h during and after CPB (n = 7). Two patients with renal failure received EACA in the manner of group III. Blood concentrations of EACA, measured by high-performance liquid chromatography, were subjected to mixed-effects pharmacokinetic modeling.**

Results: **The EACA concentration data were best fit by a model with two compartments and corrections for CPB. The elimination rate constant k_{10} fell from 0.011 before CPB to 0.0006 during CPB, returning to 0.011 after CPB. V_1 increased 3.8 l with CPB and remained at that value thereafter. Cl_1 varied from 0.08 l/min before CPB to 0.007 l/min during CPB and 0.13 l/min after CPB. Cl_2 increased from 0.09 l/min before CPB to 0.14 l/min during and after CPB. Two patients with renal failure demonstrated markedly reduced clearance. Using their model, the authors predict that an EACA loading infusion of 50 mg/kg given over 20 min and a maintenance infusion of 25 mg · kg^{-1} · h^{-1} would maintain a nearly constant target concentration of 260 μg/ml.**

Conclusions: **EACA clearance declines and volume of distribution increases during CPB. The authors' model predicts that more stable perioperative EACA concentrations would be obtained with a smaller loading dose (50 mg/kg given over 20 min) and a more rapid maintenance infusion (25 mg · kg^{-1} · h^{-1}) than are typically employed. (Key words: Antifibrinolytic therapy; coronary artery bypass grafting; coronary artery disease; fibrinolysis; pharmacokinetics.)**

ϵ-AMINOCAPROIC acid (EACA), an inhibitor of fibrinolysis, is given to patients undergoing cardiac surgery in the hope of reducing blood transfusions. EACA appears to be safe, and many studies suggest that it is an effective hemostatic agent in patients undergoing cardiac surgery (for review, see refs. 1 and 2); however, controversy persists as to its appropriate role relative to competing agents, tranexamic acid and aprotinin. We suggested that the variable efficacy of EACA from study to study could be the result of fluctuating EACA blood concentrations during surgery. We considered this likely because EACA dosing schemes were developed empirically without knowledge of EACA elimination kinetics in cardiac surgical patients and might not maintain stable and effective EACA concentrations, particularly during cardiopulmonary bypass (CPB). To better understand the effects of CPB on EACA elimination, we studied stable coronary surgery patients receiving EACA after protamine administration, as well as patients receiving EACA in the more usual fashion before, during, and after CPB. We measured EACA concentrations in blood using high-performance liquid chromatography (HPLC) and subjected those measurements to pharmacokinetic modeling, testing whether adjustments for CPB would improve model fits.[3] Finally, we used our pharmacokinetic model to propose a more rational EACA dosing scheme.

Materials and Methods

Consenting patients (n = 22) undergoing elective coronary surgery performed by a single surgeon were stud-

* Professor, Department of Anesthesiology.

† Biostatistician, Department of Anesthesiology.

‡ Laboratory Technician, Department of Anesthesiology.

§ Associate Professor, Department of Anesthesiology.

‖ Professor, Department of Cardiothoracic Surgery.

Received from the Departments of Anesthesiology and Cardiothoracic Surgery, The Wake Forest University School of Medicine, Winston-Salem, North Carolina. Submitted for publication June 18, 1998. Accepted for publication February 3, 1999. Supported by research funds of the Department of Anesthesiology, Wake Forest University School of Medicine, Winston-Salem, North Carolina. Presented in part at the 1996 and 1998 Annual Meetings of the American Society of Anesthesiologists, New Orleans, Louisiana, October 22, 1996, and Orlando, Florida, October 20, 1998. Published in ANESTHESIOLOGY as abstracts (1996; 85:A151 and 1998; 89:A533).

Address reprint requests to Dr. Butterworth: Department of Anesthesiology, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, North Carolina. Address electronic mail to: jbutter@wfubmc.edu

Table 1. Demographic Characteristics of EACA Study Patients

	Group I (30 mg/kg)	Group II (100 mg/kg)	Group III (100 mg/kg + 10 mg · kg^{-1} · h^{-1})
n	7	6	7
Age (yr)	57 ± 10	68 ± 9	67 ± 10
Sex (F:M)	1:6	3:3	2:5
Weight (kg)	85 ± 13	83 ± 21	82 ± 12

Data are incidences or mean ± SD. There were no significant differences among the groups.

EACA = epsilon-aminocaproic acid.

ied. Our study protocol was approved by the Clinical Research Practices Committee of the Wake Forest University Baptist Medial Center. Twenty patients with normal hepatic and renal function were included in our initial analysis. Each of these patients received one of two loading doses (given over 10 min) of EACA, 30 mg/kg (group I, n = 7) or 100 mg/kg (group II, n = 6) after protamine (after CPB), or a 100-mg/kg loading dose after heparin and 10 mg · kg^{-1} · h^{-1} maintenance infusion continued for 4 h (group III, n = 7). The demographic characteristics of these patients are provided in table 1. Two other patients with chronic renal failure gave their consent for blood sampling while receiving EACA, by the choice of the attending surgeon, using an infusion scheme similar to the one used in group III. These two patients were analyzed separately. The clinical characteristics of these two patients are provided in table 2.

Patients were sedated with oral diazepam (up to 10 mg) and intravenous midazolam (up to 2 mg). Peripheral intravenous and radial artery cannulae were placed after local anesthesia. General anesthesia was induced with intravenous midazolam (up to 0.15 mg/kg), fentanyl (up to 15 μg/kg), and in some cases thiopental (up to 5 mg/kg). Paralysis for tracheal intubation was obtained with intravenous succinylcholine (1 mg/kg) or pancuronium (up to 0.15 mg/kg). Anesthesia was maintained with inhaled isoflurane and intravenous fentanyl (total dose for the anesthetic up to 25 μg/kg), and paralysis was maintained with intravenous pancuronium (total dose for the anesthetic up to 0.3 mg/kg).

Cardiopulmonary bypass was conducted with hypothermia (target core temperature 28°C) using a crystalloid priming volume of 1400–1,500 ml. We used a Sarns (Ann Arbor, MI) Turbo 440 membrane oxygenator in every case. Antegrade hypothermic blood cardioplegia was used in every case, mixed 4:1 (volume of blood: volume of crystalloid cardioplegia). The typical additional (not counting the patient's blood) crystalloid cardioplegia volume was 400–450 ml. Thus, the total additional crystalloid volume from pump priming and cardioplegia was between 1,800 and 1,950 ml. At the end of CPB the contents of the venous reservoir were transferred to the patient. The remaining blood in the CPB apparatus was transferred to the Cell Saver (Haemonetics, Braintree, MA), washed, and returned to the patient. A set of timed arterial blood samples was obtained from each patient, as described in table 3. The blood samples were immediately anticoagulated with EDTA and stored on ice. After each patient's last sample had been obtained, the plasma was separated from blood

Table 2. Characteristics of Two Patients with Renal Failure Fit to a One-compartment Model

	Patient 1	Patient 2
Age (yr)	68	18
Sex	Male	Male
Weight (kg)	80	58
Preoperative creatinine (mg/dl)	4.3	16.7
Fitted parameters		
k_{10} Prebypass and postbypass	0.00120	0.00193
During bypass	0.00015	0.00182
V_1 Prebypass	43.6	16.0
During and postbypass	46.6	20.4
ξ (fixed)	1.2	1.2
Derived parameters		
Cl_1 Prebypass and postbypass	0.0523	0.0309
During bypass	0.0070	0.0371
A_u	1.0	1.0
α Prebypass and postbypass	0.00120	0.00193
During bypass	0.00015	0.00182

Table 3. Blood Sampling Times after Administration of EACA Loading Doses

Groups I and II (min)	Group III (and renal failure patients) (min)
10	10
20	30
30	60
40	120
50	180
60	240
80	270
100	300
120	360
150	420
180	600
210	720
240	NA

Times provided are the elapsed times since initiation of the EACA loading dose.

EACA = ϵ-aminocaproic acid; NA = not applicable.

cellular elements by centrifugation (1,000*g* at 4°C), and the plasma was stored at −70°C pending analysis.

Reagents

HPLC-grade acetonitrile was purchased from Sigma-Aldrich (Milwaukee, WI). HPLC-grade methanol was supplied by Burdick and Jackson (Muskegon, MI). Protein sequencing–grade phenylisothiocyanate and L-norleucine were purchased from Sigma Chemical (St. Louis, MO), to use the method of Davey and Ersser for derivatization.[4] HPLC-grade sodium acetate and sodium phosphate were purchased from J. T. Baker (Phillipsburg, NJ). Deionized distilled water was produced using a Barnstead (Dubuque, IL) purifying system. EACA was purchased from American Regent Laboratories (Shirley, NY). All other chemicals were reagent grade, or better.

Ultrafiltration

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

Derivatization

The filtered plasma (50 μl) was placed in a small glass tube (Fisher 14-923A) and dried under vacuum (Aes 1010, Savant Instruments, Holbrook, NY) for 60 min. Dry samples were then treated with 10 μl of a mixture of methanol-1M sodium acetate-triethylamine (TEA) (2:2:1, vol/vol). Samples were dried under vacuum (Savant Instruments) for 40 min. Fresh derivatization reagents, namely methanol-tetraethylammonium-water-phenylisothiocyanate (7:1:1:1, vol/vol), were added in 20-μl aliquots to each sample and were allowed to react for 20 min at room temperature. Samples were dried under vacuum for 90 min. Derivatives were reconstituted in 100 μl of 5-mM $NaHPO_4$ (at pH 7.4) acetonitrile (950:50, vol/vol). Reconstituents were transferred to clear glass conical insert tubes.

High Performance Liquid Chromatography

The chromatographic system consisted of a 600 controller, an in-line degasser, a 717+ autosampler, and a 996 photodiode array detector, all manufactured by Waters (Milford, MA). The analytical column was a NovaPak C18 (WAT086344, Waters) 3.9 × 300 mm, 4 μm, 60 Å. The mobile phase A was 70 mM $NaCH_3CO_2$ (pH 6.5) acetonitrile (975:25, vol/vol). The mobile phase B was acetonitrile-methanol-water (9:3:8, vol/vol). The eluent was delivered at a flow rate of 1 ml/min. The column temperature was maintained at 38°C by a column heater. EACA was monitored at 254 nm.

Assay Performance

Our assay technique provided linear standard curves over the range from 2.05 μg/ml to 2,050 μg/ml. Typically r^2 for linear regressions to standard curve was 0.99. The lowest concentration we have attempted for assay was 50 μg/ml; the highest concentration we have tested was 10,000 μg/ml. Standard deviations increased proportionate with measurements, permitting us to report a typical 3.6% coefficient of variation for our assay procedure.

Statistical Methods

Concentration *versus* time data were fit to two- and three-compartment 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 minimizing the extended least squares. Extended least-squares nonlinear regression uses the following maximum likelihood objective function:[5]

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

where C_i is observed EACA concentration at time i, $\hat{C}_i$ is predicted (from model) EACA concentration at time i, and var_i is expected variance at time i. The expected variance at time i includes terms reflecting both intra- and interpatient variability. The intrapatient variability was modeled as a power function:

$$var_i = \sigma^2 \hat{C}_i^{\xi}.$$

The proportionality coefficient, σ^2, is set so that the sum of the weighted residuals equals the number of observations. The power exponent ξ is estimated along with the pharmacokinetic parameters during model fitting. 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.

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

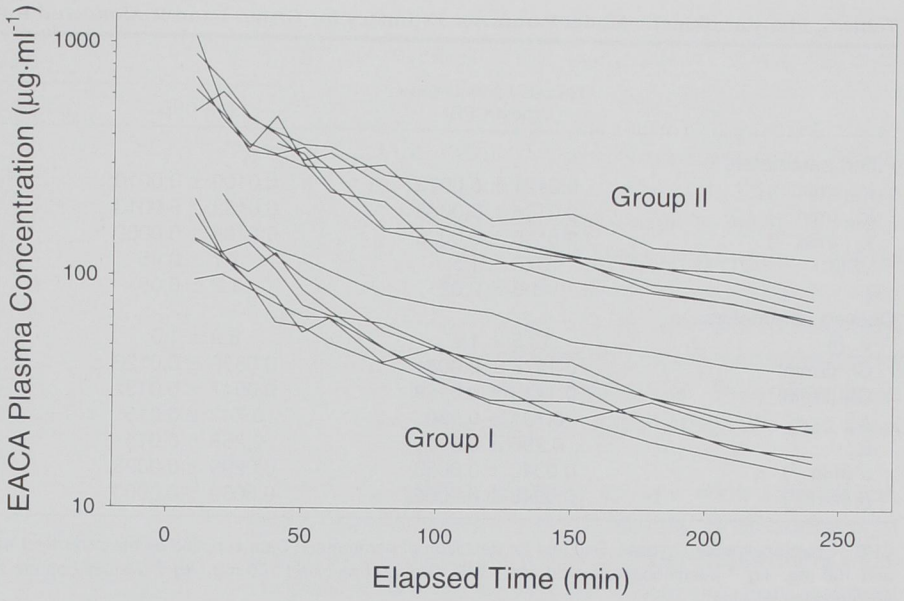

Fig. 1. Decline in plasma concentrations of ε-aminocaproic acid (EACA) after a single 30 mg/kg (group I) or 100 mg/kg (group II) dose administered after cardiopulmonary bypass (CPB). Data are plotted on a semilog scale. The two dose groups could be described by the same elimination model, confirming dose-independence of kinetics. Blood samples were collected as described in table 3.

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. Exponential coefficients and half-lives were calculated using standard equations.

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:

$$P_i = P_p e^{\eta_i},$$

where P_i is the parameter estimate of individual patient i, P_p is the population parameter estimate, and Θ_i is the random variable normally distributed with mean 0 that

Table 4. Model Selection Criteria

Model	Groups*	Objective Function	Observations (N)	Parameters (N)	SBC	AIC†	LRT†	DF†	*P* Value†
1 compartment	I and II	3540.9	164	5	−1783.20	−1775.45			
2 compartment	I and II	3346.6	164	9	−1696.25	−1682.30	194.3	4	<0.000005
2 compartment wt	I and II	3333.6	164	9	−1689.75	−1675.80			
3 compartment wt	I and II	3326.8	164	13	−1696.55	−1676.40	4.6	4	0.1468
2 compartment wt	I and II	3333.6	164	9	−1689.75	−1675.80			
2 compartment wt ξ	I and II	3310.2	164	10	−1680.60	−1665.10	23.4	1	<0.000005
3 compartment wt ξ	I and II	3305.6	164	14	−1688.50	−1666.80	4.6	4	0.33085
2 compartment wt ξ	I, II, and III	5246.5	247	10	−2650.80	−2633.25			
3 compartment wt ξ	I, II, and III	5212.8	247	14	−2644.97	−2620.40	33.7	4	<0.000005
2 compartment wt ξ	I, II, and III	5246.5	247	10	−2650.80	−2633.25			
2 compartment wt ξ CPB (V_1)	I, II, and III	5179.2	247	11	−2619.90	−2600.60	67.3	1	<0.000005
2 compartment wt ξ CPB (V_1, k_{10})	I, II, and III	5164.7	247	12	−2615.41	−2594.35	14.5	1	0.00014
3 compartment wt ξ CPB (V_1, k_{10})	I, II, and III	5158.3	247	16	−2623.23	−2595.15	6.4	4	0.17120

SBC = Schwarz-Bayesian Criterion (larger is better); AIC = Akaike Information Criterion (larger is better); LRT = log-ratio test statistic comparing model with the model immediately above; DF = degrees of freedom for LRT test; *P* values are provided only for LRT, which can only be used to compare nested models. wt = weight adjustment of V_1; ξ = power term of extended least-square error; CPB (V_1) = adjustment of V_1 for pre-CPB *vs.* CPB and post-CPB time intervals; CPB (k_{10}) = adjustment of k_{10} during CPB *vs.* pre-CPB and post-CPB time intervals. See Table 6 for a full description of the relevant adjustments to the pharmacokinetic model.

* Models based upon differing data cannot be directly compared using any of the above model selection criteria. Thus, models using data of groups I and II cannot be compared with models based upon group I, II, and III.

† AIC and LRT are included for readers more comfortable with these model selection criteria. SBC is the most parsimonious in adding model parameters and thus was our basis of model selection.

Table 5. Pharmacokinetic Model Parameter Estimates for Group I and II Alone and for Groups I, II, and III Combined

	Groups I and II Alone (post-CPB)	Groups I, II, and III Combined		
		Pre-CPB	CPB	Post-CPB
Fitted parameters				
k_{10} (min^{-1})	0.0121 ± 0.0013	0.0109 ± 0.0010	0.0006 ± 0.0013	0.0109 ± 0.0010
k_{12} (min^{-1})	0.0134 ± 0.0023	0.0123 ± 0.0013	0.0123 ± 0.0013	0.0123 ± 0.0013
k_{21} (min^{-1})	0.0135 ± 0.0026	0.0106 ± 0.0009	0.0106 ± 0.0009	0.0106 ± 0.0009
V_1^* (l)	10.6 ± 1.5	7.7 ± 0.45	11.5 ± 0.9	11.5 ± 0.9
ξ	1.3 ± 0.02	1.2 ± 0.08	1.2 ± 0.08	1.2 ± 0.08
Derived parameters				
V_2 (l)	10.5 ± 1.2	8.9 ± 1.5	13.4 ± 1.3	13.4 ± 1.3
Cl_1 (l/min)	0.1278 ± 0.0081	0.0839 ± 0.0126	0.0069 ± 0.0197	0.1256 ± 0.0057
Cl_2 (l/min)	0.1415 ± 0.0159	0.0947 ± 0.0132	0.1417 ± 0.0120	0.1417 ± 0.0120
A_u	0.704 ± 0.030	0.742 ± 0.015	0.550 ± 0.036	0.742 ± 0.015
B_u	0.296 ± 0.030	0.258 ± 0.015	0.450 ± 0.036	0.258 ± 0.015
α (min^{-1})	0.0342 ± 0.0053	0.0299 ± 0.0023	0.0232 ± 0.0022	0.0299 ± 0.0023
β (min^{-1})	0.0048 ± 0.00062	0.0039 ± 0.0003	0.0003 ± 0.0006	0.0039 ± 0.0002

CPB = cardiopulmonary bypass. See text for definition of parameters. Data supplied as the parameter estimates ± standard error. Groups I and II received 30 and 100 mg · kg^{-1} ϵ-aminocaproic acid after CPB; Group III received 100 mg · kg^{-1} ϵ-aminocaproic acid after heparinization and 10 mg · kg^{-1} · h^{-1} as a maintenance infusion.

* Based on 80-kg body weight.

accounts for interpatient variability associated with the patient.

Pharmacokinetic models were fit as two- and three-compartment models with and without the demographic covariates: age, sex, height, weight, body surface area, body mass index, and preoperative creatinine concentration. 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, can be modeled with indicator covariate, I_{CPB}, as follows:

$$K = \theta_1 + \theta_2 \cdot I_{CPB}$$

where θ_1 and 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:

$$K = \theta_1 \quad \text{pre- and post-CPB}$$
$$K = \theta_1 + \theta_2 \quad \text{during CPB}$$

Thus, as shown previously, K can be modeled to increase by θ_2 during CPB. If K 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 θ_2 will include 0). In similar manners, indicator covariates can be added for the pre-CPB or post-CPB phase.

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

$$K = \theta_1 + \theta_2 \cdot I_{high}$$

where θ_1 and θ_2 are model-estimated parameters,

$$I_{high} = \begin{cases} 0: & \text{for observations from patients receiving the 30 mg/kg bolus infusion} \\ 1: & \text{for observations from patients receiving the 100 mg/kg bolus infusion.} \end{cases}$$

Thus, if K is not dose-dependent then θ_2 should not differ statistically from 0.

Confidence limits of parameters and the Schwarz-Bayesian criterion (SBC) were used to determine which models best fit the data.[6] Graphs showing model fits were used to confirm these choices.

All other analyses were accomplished using the SAS Program, version 6.12 (SAS Institute, Cary, NC) with $\alpha < 0.05$ considered significant.

Results

EACA was rapidly eliminated after the two loading doses of groups I and II (fig. 1). The SBC determined that a more complex three-compartment model was not preferred over the two-compartment model, so two-compartment model estimates are reported (tables 4 and 5).

Table 6. Best Fit Two-compartment Parameter Estimates (±SE)* with Adjustments for Effects of Cardiopulmonary Bypass (CPB) and Weight (wtkg)

$k_{10} = 0.0109\ (\pm 0.0010) - 0.0103\ (\pm 0.0017) \cdot I_{CPB}$
$k_{12} = 0.0123\ (\pm 0.0013)$
$k_{21} = 0.0106\ (\pm 0.0009)$
$V_1 = 0.144\ (\pm 0.011) \cdot \text{wtkg} - 3.82\ (\pm 0.87) \cdot I_{preCPB}$
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 interpatient coefficients of variability were estimated as 0.13, 0.18, 0.10, and 0.16 for k_{10}, k_{12}, k_{21}, and V_1, respectively.

The pharmacokinetic models were first fit to the data of groups I and II combined. The best model fit adjusted V_1 for weight by estimating $V_1 = 0.13 \cdot$ body weight in kilograms (table 6). The inclusion of dosing-group indicator covariates for each model parameter did not improve model fits, thus supporting the assumption that the model rate constants and V_1 were dose-independent.

Despite the maintenance infusion, EACA concentrations were not maintained at a constant value in group III (fig. 2). To better understand the possible effects of CPB on EACA elimination, models were fit to all the data from groups I, II, and III combined, with time-dependent covariates indicating perioperative time period (see table 4). These time-dependent covariates were used to determine whether any of the model parameters should have adjustments before, during, or after CPB. Table 4 provides the statistical justification for our sequential decisions to select a two-compartment model over a one-compartment model and a weight-adjusted two-compartment model over a two-compartment model without a weight adjustment, to reject a three-compartment model with weight adjustment in favor of a two-compartment model with weight adjustment, and to select a three-compartment model with adjustment for weight and error structure (ξ, as discussed in Methods) over two-compartment models or a three-compartment model without the same adjustment. Note that these initial comparisons were all made using only data from groups I and II.

When data from all three groups were considered, additional corrections were indicated. With addition of data from group III, the various three-compartment models proved to have smaller SBCs than two-compartment models with CPB-related adjustments in weight, ξ, V_1 and k_{10}. Adjustments in other pharmacokinetic parameters and other covariates were also tested; however, they did not improve the model. We have not included all these other tests on table 4 for simplicity.

Our best model fit, based on confidence intervals and the SBC (and confirmed graphically), included adjustments for k_{10} and V_1 (see table 5). The elimination rate constant, k_{10}, declined 10-fold during CPB, with its best rate estimate being 0.0109 before CPB, becoming 0.0006 during CPB, and returning to 0.0109 after CPB. Volume of distribution increased 3.8 l at onset of CPB and re-

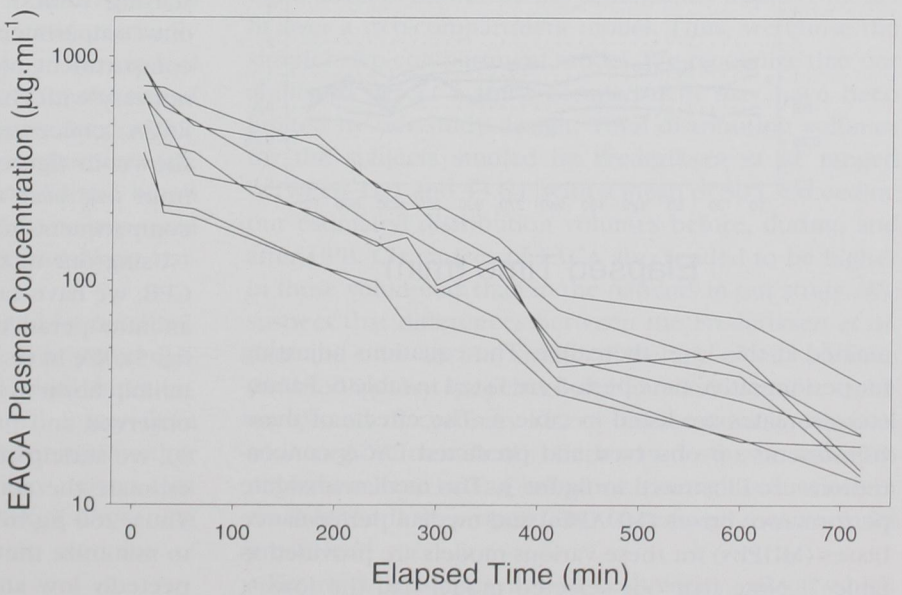

Fig. 2. Decline in plasma concentrations of ε-aminocaproic acid (EACA) in group III after a 100 mg/kg loading dose and 10 $mg \cdot kg^{-1} \cdot h^{-1}$ maintenance infusion, the latter continued for 4 h. Data are plotted on a semilog scale. Blood samples were collected as described in table 3. The times of cardiopulmonary bypass are indicated on the figure with dotted lines.

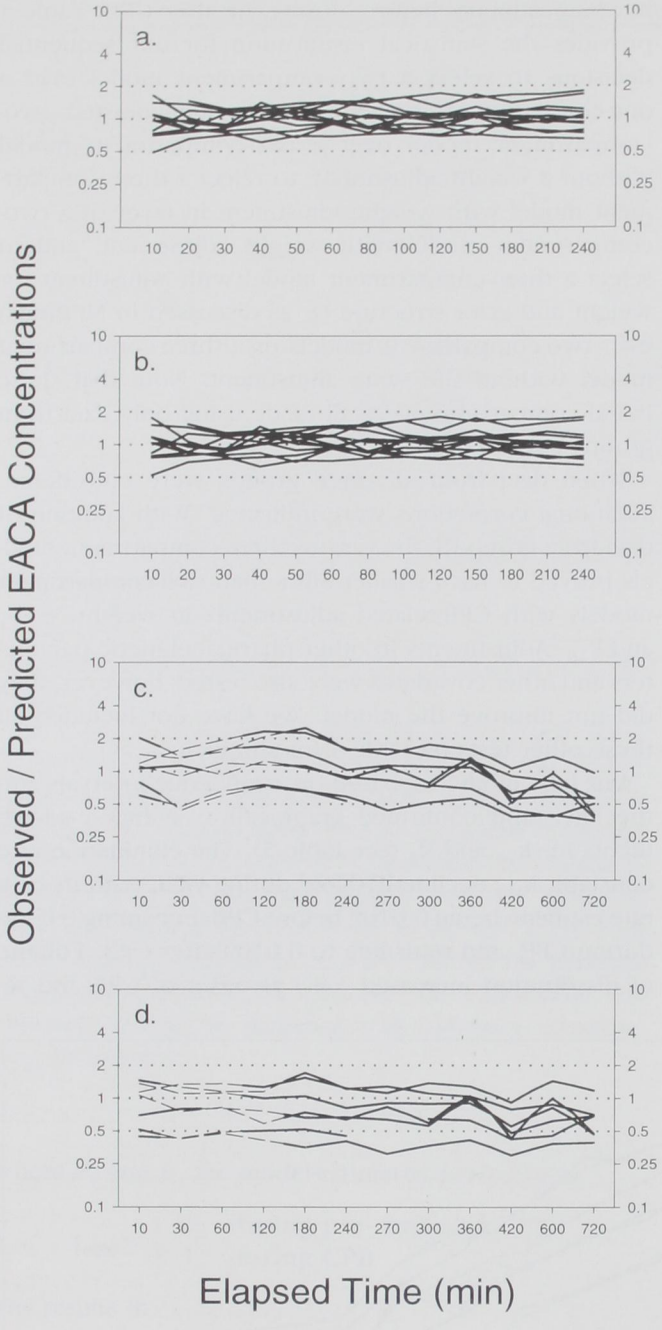

Fig. 3. Observed and predicted ϵ-aminocaproic acid (EACA) concentrations for the patients in groups I and II using a model based on data from groups I, II, and III either without (*A*) or with (*B*) corrections for the effects of cardiopulmonary bypass (CPB), as described in the text and table 4. Observed and predicted EACA concentrations for group III are provided using the model based on data from groups I, II, and II without CPB corrections (*C*) and using the same data with CPB corrections (*D*). Data are plotted on a semilog scale. Dashed line = time of CPB. CPB corrections had little effect on model predictions for groups I and II, in which EACA was administered after CPB. Conversely, the CPB corrections significantly improved model predictions in group III, in which EACA was administered before, during, and after CPB. Time along the abscissa is measured from administration of the loading dose in all cases. Note that observed and predicted value curves are "flatter" in *D* than in *C*, confirming a more consistent fit. A simple explanation for the seemingly parallel line is variability in EACA volumes of distribution.

mained at this level thereafter. The equations adjusting for perioperative time period are listed in table 6. Parameter estimates are listed in table 4. The effects of these adjustments on observed and predicted EACA concentrations are illustrated in figure 3. The median absolute performance errors (MDAPEs) and median performance biases (MDPBs) for these various models are provided as table 7. Note that our selected model had the lowest MDPB (−0.4%) and a low MDAPE of 21.8%. Ninety-five percent of our predictions from our final CPB model had an MDAPE of less than 81.4%. In contrast our best two-compartment or three-compartment models had 95th percentiles in MDAPE of 150% and 192%, respectively.

We attempted to fit the EACA blood concentrations from the two patients with renal failure to the two-compartment model with adjustments for perioperative phase, as described previously. The model fits developed for these two patients converged erratically to a two-compartment model and gave widely diverging parameter estimates on different runs (*i.e.*, we obtained markedly different parameter estimates with small changes in starting values); therefore, we fit these patients to a one-compartment model (see table 2). With the one-compartment model the final parameter estimates did not vary with changes in initial parameter estimates. The EACA concentrations *versus* time observations are shown in figure 4 with the predicted concentrations from our best non-renal failure model and the one-compartment model developed for each patient.

Using our mixed effects model with adjustments for CPB, we have calculated a dosing technique that targets an intraoperative EACA concentration of 260 μg/ml (see fig. 5). We have assumed that 130 μg/ml will completely inhibit fibrinolysis[7]; however, based on our graphs of observed and predicted EACA concentrations (see fig. 3), we anticipate that our model prediction could overestimate the actual concentration by as much as 50%. Thus, 260 μg/ml might be the more conservative target to minimize the likelihood of a patient having an unexpectedly low and potentially ineffective EACA concen-

Table 7. Performance Error (%) for Selected Pharmacokinetic Model Fits

Data Set	Pharmacokinetic Model	Median APE	95th Percentile of APE	Median PB
Groups I and II only	2-compartment	21.5	80.4	−2.3
	2-compartment wt	21.5	80.4	−2.3
	3-compartment wt	17.3	90.1	3.3
	2-compartment wt ξ	17.5	78.9	0.7
	3-compartment wt ξ	17.1	77.0	−0.5
Groups I, II, and III	2-compartment wt ξ	21.9	150.2	−7.4
	3-compartment wt ξ	24.7	191.7	6.4
	2-compartment wt ξ CPB (V_1)	21.5	155.1	−7.5
	2-compartment wt ξ CPB (k_{10})	19.	92.3	−2.8
	2-compartment wt ξ CPB (V_1, k_{10})	21.8	81.4	−0.4
	3-compartment wt ξ CPB (V_1, k_{10})	21.5	80.4	−2.3

Median APE = median absolute performance error; APE = absolute performance error; Median PB = median performance bias; wt = weight adjustment of V_1; ξ = power term of extended least-square error; CPB (V_1) = adjustment of V_1 for pre-CPB *vs.* CPB and post-CPB time intervals; CPB (k_{10}) = adjustment of k_{10} during CPB *vs.* pre-CPB and post-CPB time intervals.

$$\text{Absolute performance error (APE)} = \left|\frac{\text{observed} - \text{predicted}}{\text{predicted}}\right| \times 100\%$$

$$\text{Performance bias (PB)} = \frac{\text{observed} - \text{predicted}}{\text{predicted}} \times 100\%$$

Note that the model selected (2-compartment wt ξ CPB (V_1, K_{10}) had the median performance bias that was closest to zero and had among the lower median absolute performance errors and among the lower 95th percentile absolute performance errors.

tration. We assume that a certain concentration must be exceeded in *all* patients for consistent efficacy, but we recognize that this is an untested hypothesis.

Discussion

Our data demonstrate that EACA is rapidly distributed and eliminated in patients undergoing aortocoronary bypass surgery. CPB increases the volume of distribution of the central compartment (V_1) by 3.8 l and markedly decreases the elimination rate constant k_{10}. The standard error for this k_{10} during CPB (0.0013) is twice the size of its estimate (0.0006 min^{-1}), which includes the possibility that k_{10} is 0 during CPB. In any case, our best estimate is that k_{10} *approaches* 0 during CPB. Additional blood samples before and during CPB would have improved the quality of our parameter estimates and likely narrowed the confidence limits.

EACA kinetics were markedly prolonged by renal failure in our two patients (neither of whom required dialysis) relative to patients with normal renal function. Given the concern about potential renal injury from EACA, clinicians might choose to infuse aprotinin rather than EACA in patients with renal failure, given that aprotinin appears not to increase the risk of worsening renal failure in patients with preexisting elevation of serum creatinine concentrations.[8–10]

Previous studies of EACA pharmacokinetics were performed in volunteers, not in patients undergoing cardiovascular surgery.[7,11] The drug is known to be largely excreted by the kidneys, with a clearance approaching that of creatinine. Frederiksen *et al.*[7] fit EACA concentration *versus* time data from volunteers to a three-compartmental model but provided no statistical justification for this choice. We found that the three-compartment model did not significantly improve model fit over a two-compartment model. Thus, we chose the simpler two-compartment model. We recognize that our ability to detect a third compartment may have been limited by our study design. Total distribution volumes for the subjects studied by Frederiksen *et al.* ranged between 21.1 and 43.6 l, with a mean of 30 l, exceeding our estimated distribution volumes before, during, and after CPB. Clearances of EACA also tended to be higher in these volunteers than in the patients in our study. We suspect that differences between the Frederiksen *et al.* data and ours are the result of the age of our patients (with obligatory age-related declines in creatinine clearance), and of coronary artery disease (and its medical and surgical treatment). General anesthesia and CPB might also have had an influence, through reductions in renal blood flow proportional to reduced mean arterial pressure.[12]

Figure 5 illustrates dosing techniques, all of which

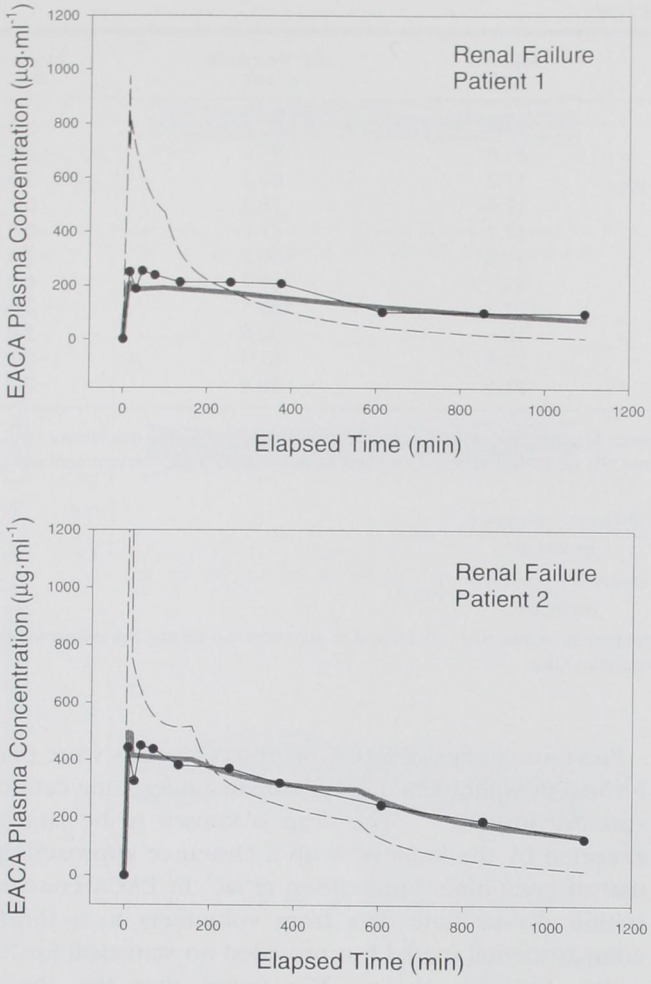

Fig. 4. Observed and predicted ϵ-aminocaproic acid (EACA) concentrations for two patients with renal failure. Note that the best model fit from patients without renal failure (indicated with a dashed line) overestimates the actual concentration achieved after the loading dose, consistent with an increased volume of distribution, but underestimates the EACA concentration later, consistent with reduced EACA clearance in renal failure. Solid lines = individual model fits to a one-compartment model (see table 2 for details).

have been reported to be effective at reducing perioperative bleeding, that yield markedly differing blood concentrations of EACA.[13–20] Using our best model with adjustments for the effects of CPB, we have modeled the EACA concentrations that would be produced by these dosing schedules (see fig. 6). It is notable that none of these dosing schedules yield constant intraoperative EACA concentrations in blood. It is of note that no study of EACA efficacy has determined rigorously whether this agent might increase the risk of arterial or venous thrombosis, perioperative stroke or neuropsychological deficits, renal failure, or myocardial infarction and, in particular, whether the risk for these worrisome side effects might increase with increasing concentrations of EACA.[8,9,21,22] Unfortunately, such outcome studies will likely never be done because they would be extremely expensive, and EACA has long been an inexpensive generic product. If we assume that EACA concentrations must exceed the IC_{50} to prevent clot lysis during and after CPB, then all of the reportedly efficacious dosing techniques could be improved upon.[7,13] We have used our pharmacokinetic model to develop a dosing scheme to maintain stable EACA concentrations before, during and after CPB. Such dosing schemes could permit an investigator to define the EACA concentration threshold for efficacy and might reduce the likelihood that excessively high concentrations, with their anticipated greater risks of adverse events, would be produced.

Our results could indicate adjustment of clinical EACA dosing. Dosing regimens proposed by many authors do not result in constant plasma concentrations of EACA. If a constant concentration is desirable to maintain constant effect (and we recognize that this assumption is beyond the scope of the present study), then published dosing schemes would be less effective than a regimen based on our kinetic results. Because EACA efficacy studies have not been conducted with knowledge of this agent's pharmacokinetics, the appropriate target concentration is not clear. Frederiksen *et al.*[7] monitored clot lysis in whole blood and platelet-rich plasma in six volunteer subjects. Assuming a single binding site without cooperativity, these investigators used the Hill equation to define an EACA IC_{50} for inhibiting fibrinolysis (median value 73.4, range 37.3–82.1 μg/ml). Maximal efficacy would likely be achieved by concentrations two- to four-fold greater than the IC_{50}. Thus the suggestion of 130 μg/ml by McNicol *et al.*[11] does not conflict with the findings of Frederiksen *et al.*[7]

We recognize that we have not actually tested our model using blood concentration data from these other dosing schemes: Our conclusions about other dosing schemes were obtained from modeling, not from actual experimentation. Nevertheless, we note that blood concentrations reported by Bennett-Guerrero *et al.*[14] are consistent with our model predictions, as depicted on the relevant part of figure 5. We also recognize that EACA may reduce perioperative bleeding by a mechanism other than fibrinolysis, and that another mechanism might well have a differing concentration threshold for efficacy.

Our conclusions about the effects of CPB are based

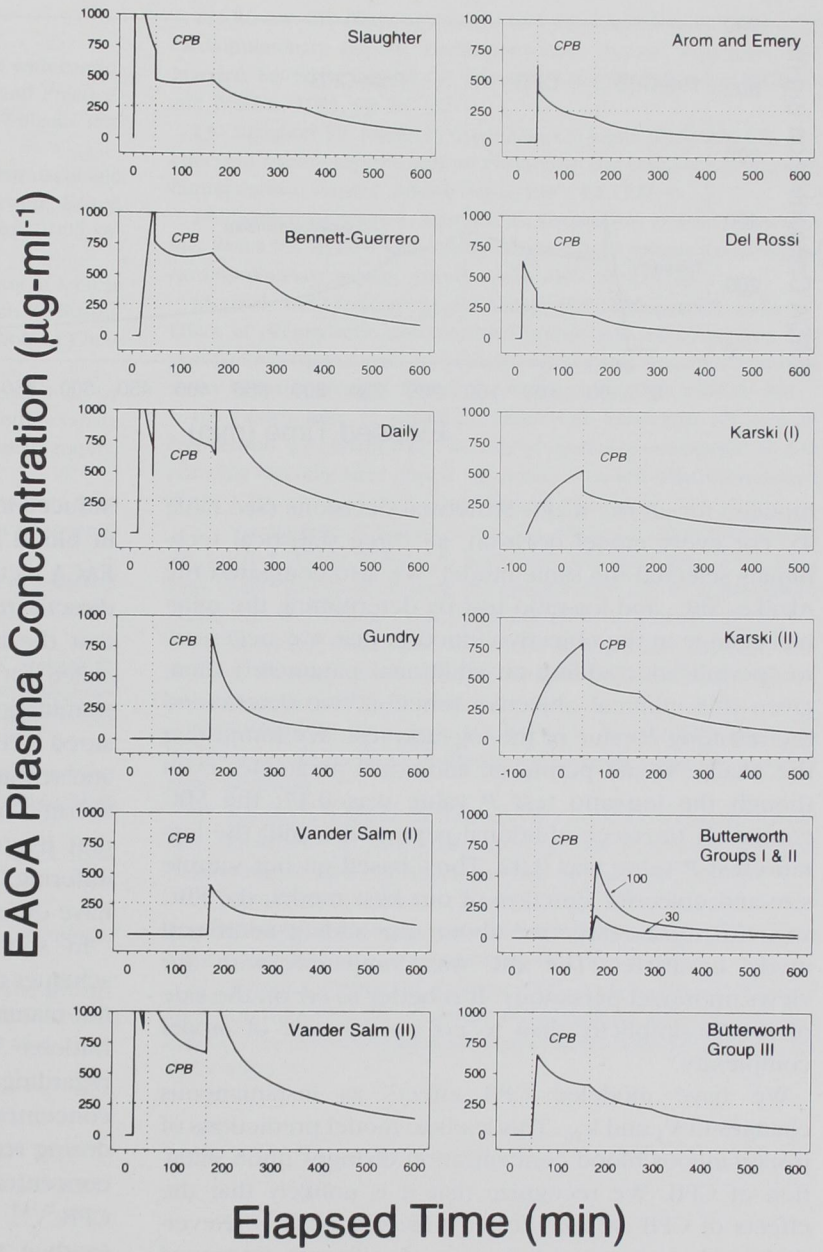

Fig. 5. ϵ-Aminocaproic acid (EACA) concentrations from a variety of published EACA dosing techniques, predicted using our best pharmacokinetic model with adjustments for the effects of cardiopulmonary bypass (CPB). For simplicity, we assumed a patient weighing 80 kg with normal renal function and assumed that 45 min of surgery would take place before and after 2 h of extracorporeal circulation. Note that these dosing techniques produce a wide range of plasma concentrations. A dotted line indicates 260 mg/kg, which is twice the effective concentration (see text for details).[11] Slaughter *et al.*[13] administered 150 mg/kg before induction of anesthesia, with a maintenance infusion of 15 mg · kg^{-1} · h^{-1} continuing until 3 h after CPB. Bennett-Guerrero *et al.*[14] administered 150mg/kg over 30 min after induction of anesthesia, and 0.75 mg · kg^{-1} · h^{-1} for 4 h thereafter. Daily *et al.*[15] administered three 10-g doses, after induction of anesthesia but before skin incision, after heparin administration into the CPB pump, and after administration of protamine. Gundry and colleagues (who described their technique in the discussion accompanying Daily *et al.*[15] gave 10 mg EACA immediately after CPB. Vander Salm and colleagues[16,17] have described several techniques. In one, 5 g was administered over 5 min immediately after CPB, followed by 1 g/h for 6 h.[16] The second included three 10-g doses of EACA: before skin incision, after heparin administration, and before protamine immediately after CPB.[17] Arom and Emery[18] gave a single 5-mg/kg dose before initiation of CPB. DelRossi *et al.*[19] gave 5 g prior to skin incision and 1 g/h for 6 h thereafter. Karski *et al.*[20] also described two dosing techniques. In one, patients received a 10-g dose of EACA as an intravenous infusion, completed immediately prior to CPB. In the other, patients received a 15-g dose of EACA as an intravenous infusion, completed immediately prior to CPB. In the present study, group I received 30 mg/kg after protamine, group II received 100 mg/kg after protamine, and group III received 100 mg/kg and a 10 mg · kg^{-1} · h^{-1} maintenance infusion (for 4 h) initiated when heparin was administered for CPB.

primarily on the data from the seven patients who first received EACA prior to CPB, in comparison with the data from the remaining 13 patients who first received EACA after CPB. We recognize that we would have obtained a better assessment of the effects of CPB on EACA kinetics had we chosen to put all our subjects in group III. On the other hand, groups I and II provided "cleaner" data with which to test for dose-dependence of kinetics and with which to compare two- and three-compartment models. We have made conclusions about the effects of renal function on EACA elimination based on only two patients. However, once controversy arose about EACA and renal injury, it seemed unreasonable for us to collect additional data about EACA in such patients.[8]

Model selection criteria are based on asymptomatic theory and thus are only approximate. Because different authors use differing statistical techniques to determine the optimal complexity of pharmacokinetic models, we calculated the Akaike Information Criterion, SBC, and log-ratio test (LRT) *P* values (when comparing nested

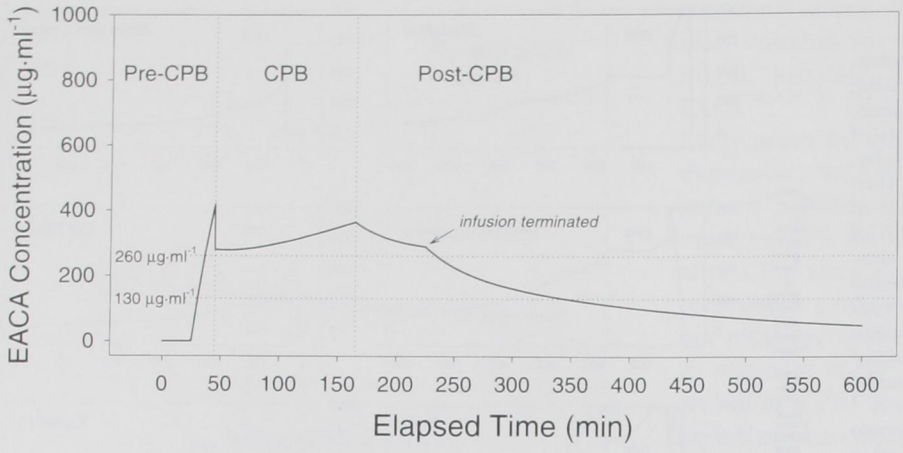

Fig. 6. Simulated dosing techniques to reliably exceed an ϵ-aminocaproic acid (EACA) concentration of 130 μg/ml. The simulated 80-kg patient received 50 mg/kg as a loading infusion for 20 min prior to cardopulmonary bypass (CPB) and then received a 25 mg · kg^{-1} · h^{-1} maintenance infusion, starting at CPB and maintained for 3 h thereafter. Based on the patient-to-patient variability illustrated in figure 3, we have targeted 260 μg/ml (twice the effective concentration), so that < 5% of patients will have a concentration < 130 μg/ml. Note that the typical patient will maintain EACA concentrations ≥ 130 μg/ml for nearly 2 h after the infusion is discontinued.

models) for all the major structural decisions (see table 4). For every model decision, all three statistical techniques selected the same model. We also compared the Akaike, SBC, and log-ratio test by determining the minimal change in the objective function that was necessary to "permit" our adding an additional parameter; then, given this minimal objective function, we determined the resulting *P* value of the log-ratio test. We found that the Akaike would permit an additional parameter even though the log-ratio test *P* value was 0.17; the SBC continued to reject additional parameters until the log-ratio test *P* value was 0.02. Thus, based on our sample size and objective function of our best model, the SBC was the most restrictive about our adding additional model covariates. The SBC was compatible with our views on model parsimony: It is better to err on the side of model simplicity than to err on the side of model complexity.

We have modeled CPB effects as instantaneous changes in V_1 and k_{10}. This leads to model predictions of instantaneous blood concentration changes upon initiation of CPB. We recognize that it is unlikely that the effects of CPB are manifested this way *in vivo*. Nevertheless, these simple adjustments significantly improved the efficiency with which we could model the blood EACA concentrations in patients undergoing CPB during this infusion, as confirmed by SBC (see fig. 3). Further research could determine whether a more complex adjustment to our model parameters would provide an even more efficient fit to the data. We also recognize that patients are likely to have greater blood loss if they are heparin-anticoagulated than if they are not anticoagulated, and that most patients have considerable blood loss during the first few hours after CPB. Thus, some of the effects that we have modeled as a result of a CPB-induced increase in V_1 may, in part, result from drug loss in blood suctioned from the surgical field, binding of EACA to the CPB apparatus, or some other process not directly related to CPB *per se*. This may be the reason that the best model fit for our V_1 correction for CPB called for the correction to continue unchanged after termination of CPB. We also recognize that our measured CPB effects, recorded during hypothermia (28°C) and rewarming, might not necessarily apply to normothermic or near-normothermic CPB. Indeed, it is likely that hypothermia *per se* alters EACA kinetics. Finally, differing CPB apparatus and priming solutions might also have different effects on EACA kinetics.

In summary, our data confirm that EACA dosing schemes (reported in previous EACA efficacy studies) do not maintain stable intraoperative EACA plasma concentrations. We are reluctant to make recommendations regarding an optimal dosing technique in the absence of concentration *versus* efficacy data. Nevertheless, most dosing regimens provide sustained intraoperative EACA concentrations in the 250–790 μg/ml range during CPB.[8–15] The dosing technique illustrated in figure 6 (with a target concentration of 260 μg/ml), using a 20-min loading dose of 50 mg/kg prior to CPB and a maintenance infusion of 25 mg · kg^{-1} · h^{-1}, would maintain EACA concentrations in the effective concentration range with less deviation than would be anticipated from other reported dosing techniques. This dosing technique would also provide concentrations well above those recommended by Frederiksen *et al.*[7] and by McNicol *et al.*[11]

The authors thank Miyuki Nakayama Shouse for performing most of the EACA assays.

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