

CME Antifibrinolytic Therapy in Surgery for Congenital Heart Disease

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The efficacy of the serine protease inhibitor, aprotinin, and the lysine analogs, ϵ -aminocaproic acid and tranexamic acid, in reducing bleeding and transfusion in adults undergoing cardiac surgery is well established. Although children undergoing cardiac surgery are clearly at high risk for bleeding and transfusion, the risks and benefits of this therapy for the pediatric population are less well understood. There is a reasonable body of literature examining antifibrinolytic therapy in congenital heart surgery, but the large variability in patients studied, procedures, methods, and dosing schemes makes a quantitative analysis of this literature impractical. A qualitative review of this literature reveals significant support for the efficacy of all three drugs for decreasing bleeding and transfusion in congenital heart surgery, likely with more benefit in certain populations. Limited data suggest that there is no difference in efficacy among the three drugs, although aprotinin may have unique antiinflammatory effects that are of benefit in pediatric patients. There is not enough evidence to draw any conclusions about the safety of these drugs in children, although it appears that the risk of anaphylaxis with aprotinin in children may be less than in adults. Dosing schemes used for these drugs have been variable and not always based on sound pharmacologic principles, despite available pharmacokinetic and pharmacodynamic data. Further research should be directed toward establishing safety, evaluating the relative efficacy of the two classes of drugs, proving benefit in specific patient groups, and better defining effective dosing schemes.

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Cardiopulmonary bypass (CPB) and cardiovascular surgery activate coagulation, inflammation, and fibrinolysis, which often have deleterious effects on patient outcomes.^{1,2} Early in clinical experience with CPB, attempts were made to modify these effects with both lysine analog antifibrinolytics³ and aprotinin.⁴ Pediatric patients are especially at risk for hematologic derangement related to CPB,⁵ as they have several unique characteristics that increase their risk for bleeding. Because an infant's blood volume is much smaller than that of the prime in the CPB circuit, hemodilution alone produces impaired hemostasis related to dilutional effects.^{2,5,6} This dilution is compounded by the immaturity of the neonatal immune system. Newborn plasma has 30%–70% lower levels of both procoagulant and anticoagulant proteins than adult levels.^{7–9} In addition to quantitative differences,

several neonatal coagulation proteins, such as plasminogen and fibrinogen, have structural differences from their adult forms.^{8,9} Both qualitative¹⁰ and quantitative¹¹ abnormalities in coagulation proteins have significant functional sequelae, which influence the hematologic responses to CPB and interact with antifibrinolytics and aprotinin. Congenital heart disease (CHD) itself has long been associated with coagulation abnormalities,¹² including platelet abnormalities^{13,14} and fibrinolysis.^{15–17} As a result, bleeding is more common in pediatric cardiac surgery patients than in adults.¹⁸ Bleeding is an outcome to be avoided, as it is associated with hemodynamic instability,¹⁹ prolonged surgical times, reoperation,^{20–23} and increased need for allogeneic transfusions.²³ Although the risk of viral disease transmission has decreased with more thorough testing of the blood supply, other adverse effects of transfusion remain, such as transfusion reactions, immune modulation, impairment of microvascular flow, and even mortality.^{18,24}

There is extensive published research on the use of aprotinin and lysine analog antifibrinolytics to modify the adverse effects of CPB in adults.^{25,26} Efficacy in decreasing bleeding and transfusion is well established, as noted by the recent guidelines published by the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists.²⁷ Although the safety and efficacy of aprotinin has been extensively studied

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Table 1. Lysine Analogs Studies

Study	Year	Jadad	N	Age	Bleed	Trans	Other	Load (mg/kg)	Infusion (mg/kg/h)	Prime (mg/kg)
ε-Aminocaproic acid										
McClure ⁵³	1974	4	56	>2 yr	+			75	15	510 mg/unit RBC
Williams ⁵⁶	1999		140	1–16 yr	+	–	RE(+); PV(–)	150	30	0
Rao ⁵¹	2000	3	170	2 mo–14 yr	+	+	CT; RE(+)	100 ^c	0	100
Chauhan ²³	2000	2	140	2 mo–14 yr	+	+	CT(–); RE(+)	100 ^c	0	100
Chauhan ²²	2004 ^a	1	100	2 mo–14 yr	+	+	CT; RE(+)	100 ^c	0	100
Tranexamic acid										
Zonis ⁵⁴	1996	5	82	1 d–14 yr	+ / – ^b	+ / – ^b		50	0	0
Reid ²⁰	1997	4	41	6 mo–12 yr	+	–	CT, \$(+); PV(–)	100	10	100
Levin ⁵⁵	2000	4	56	1 d–16 yr	–	–		50	0	0
Chauhan ⁵⁰	2003	1	120	2 mo–14 yr	+	+	CT; RE(+)	10 ^c	0	10
Chauhan ²¹	2004	1	150	2 mo–15 yr	–	–	RE(–)	50	0	0
					+	+	RE(+)	10	1	0
					+	+	RE(+)	10 ^c	0	10
					+	+	RE(+)	20 ^c	0	0
Chauhan ²²	2004 ^a	1	100	2 mo–14 yr	+	+	CT; RE(+)	10 ^c	0	10
Bulutcu ⁵²	2005	2	50	2 mo–9 yr	+	+	CT(+)	100 ^c	0	100

All are randomized controlled trials, except Williams,⁵⁶ which is a retrospective case-control study.

Jadad = Study quality as described by Jadad²³; 0 (poor)–5 (good).

Bleed = blood loss at 24 h; Trans = transfusion of red blood cells and/or products; + = significant benefit versus control; – = no benefit. Other is other reported outcomes including time required for chest closure (CT), RE = Reexploration for bleeding; PV = Postoperative ventilation time; and cost (\$) = Red blood cells.

^a This was a three-group study: ε-aminocaproic acid, Tranexamic acid, placebo; results shown as each drug versus placebo.

^b Significant benefit only in *post hoc* sub-group of cyanotic patients.

^c This dose was repeated after weaning from cardiopulmonary bypass.

in randomized placebo-controlled studies,²⁶ recent reports from observational databases have raised questions.^{28,29} As with many pharmacologic therapies, however, the literature on pediatric use of these drugs is significantly less complete, and issues of efficacy, safety, and even dosing remain.

The goal of this review is to evaluate the published literature on the efficacy, safety, and dosing of lysine analogs and aprotinin to attenuate adverse effects of cardiac surgery and CPB on bleeding and transfusion requirements in pediatric patients.

METHODS

Ovid and Pubmed searches were performed using the terms: aprotinin, ε-aminocaproic acid (EACA), tranexamic acid (TA), antifibrinolytic, and pediatric, child, neonate, infant, and CHD. References of more recent articles were hand-searched for additional studies. Fifty-two studies and case reports reporting the effects of aprotinin and lysine analogs in pediatric cardiac surgery were reviewed. Particular attention was given the 22 randomized controlled trials (RCT) of aprotinin, EACA, and TA. Review of these showed that quantitative analysis of the combined data (i.e., a meta-analysis) was not practical due to the various and inconsistent outcome measures reported as well as the inconsistent reporting of the variability of the data. Therefore this review is qualitative in nature.

The overall methodological quality of the studies was fair to poor, with many lacking appropriate

blinding and most omitting a discussion of withdrawals and dropouts. Jadad scores for appropriate methodological design, to avoid the risk of bias, were calculated as previously described³⁰ and are included in Tables 1 and 2.

The Lysine Analogs: EACA and TA

EACA and TA are analogs of the amino acid lysine (Fig. 1). They are thought to exert their antifibrinolytic effect by interfering with the binding of plasminogen to fibrin,³¹ which is necessary for activation of the pro-enzyme to its active form, plasmin. TA may also improve hemostasis by preventing plasmin-induced platelet activation.³² Both TA and EACA appear to have antiinflammatory properties^{33,34} but not to the same extent as aprotinin.³⁵ Both drugs have been in clinical use for decades and have been shown to decrease bleeding and need for transfusion associated with adult cardiac surgery.^{25,36,37}

EACA is Food and Drug Administration (FDA) approved for “enhancing hemostasis when fibrinolysis contributes to bleeding.”³⁸ The package insert specifically states that fibrinolytic bleeding may be associated with heart surgery. Current acquisition cost is \$1–2 for a 5-g vial. It is eliminated almost entirely by the kidneys with a terminal elimination half-life of about 2 h in healthy adults.³⁹

TA is approximately 10 times more potent as an inhibitor of fibrinolysis than EACA.^{40,41} The FDA-approved indication for TA is for the short-term

Table 2. Randomized Controlled Studies of Aprotinin versus Placebo

Study	Year	Jadad	N	Age	Bleed	Trans	Other	Load (KIU/kg)	Infusion (KIU/kg/h)	Prime (KIU/kg)
Huang ⁶⁵	1993	2	30	24 mo–10 yr	+	NR		35–50,000	3.5–5	6.5–7.5 × 10 ⁵
Dietrich ⁶³	1993	2	60	22 d–21 mo	–	–		15,000	0	15,000
					+	–		30,000	0	30,000
Boldt ⁵⁹	1993	1	42	13 ± 8 mo	–	–		20,000	20,000 ^b	20,000
					–	–		35,000	10,000	35,000
Boldt ¹⁹	1993	1	48	3 d–16 mo	–	^a		25,000	25,000 ^c	25,000
				21–70 mo	^a	^a		25,000	25,000 ^c	25,000
Herynkopf ⁶⁴	1994	3	30	8 mo–11 yr	–	+	SD; CT(–)	20,000	10,000	20,000
Boldt ⁶⁰	1994	1	30	33 ± 9 mo	–	–		30,000	30,000 ^b	30,000
Seghaye ⁶⁷	1996	1	25	9 mo–12 yr	–	–	PV(–)	10,000	0	10,000
D'Errico ⁶²	1996	4	57	4 mo–12 yr	–	+	SD, \$(+)	1.7 × 10 ⁶ /M ²	4 × 10 ⁵ /M ²	1.7 × 10 ⁶ /M ²
Davies ⁶¹	1997	5	42	1 d–10 yr	–	–	CT(–); SD(+)	1–1.7 × 10 ⁶ /M ²	4–5 × 10 ⁵ /M ²	1–1.7 × 10 ⁶ /M ²
Miller ⁶⁶	1998	0	45	5–14 mo	–	+	\$, CT, PV(–)	20,000	10,000	20,000
					–	+	\$, CT(+), PV(–)	40,000	20,000	40,000
Wipperman ⁶⁸	1999	3	34	6 d–15 yr	NR	–		28,000	7000	28,000
Chauhan ²³	2000	2	180	2.5 mo–13 yr	+	+	CT(–)	10,000	10,000	10,000
Mossinger ⁶	2003	4	60	2 d–1 yr	+	+	PV(+)	30,000	0	500,000 KIU
Bulutcu ⁵²	2005	2	50	2 mo–9 yr	+	+	CT(+)	30,000	0	30,000 ^c

Age is given as range or mean ± standard deviation.

Jadad = Study quality as described by Jadad²³; 0 (poor)–5 (good); Bleed = blood loss at 24 hours.

Trans = transfusion of red blood cells and/or hemostatic products; + = treated patients showed benefit relative to controls; – = no benefit was shown; NR = not reported; Other is other reported outcomes including surgeon's subjective evaluation of "dryness" of the wound (SD), CT = time required for chest closure; PV = Postoperative ventilation time; and total hospital cost (\$); KIU = kallikrein inhibiting units.

^a Placebo group had less bleeding and transfusion than treated group.

^b This dose was given as an hourly bolus rather than a continuous infusion.

^c This dose was repeated after weaning from bypass.

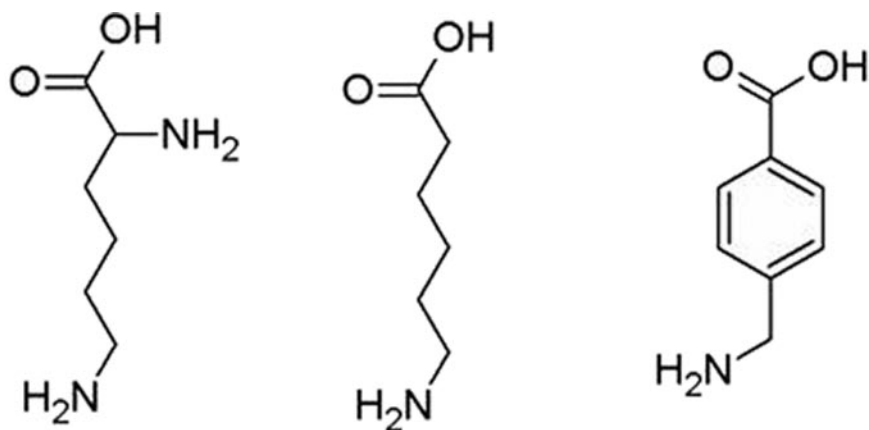
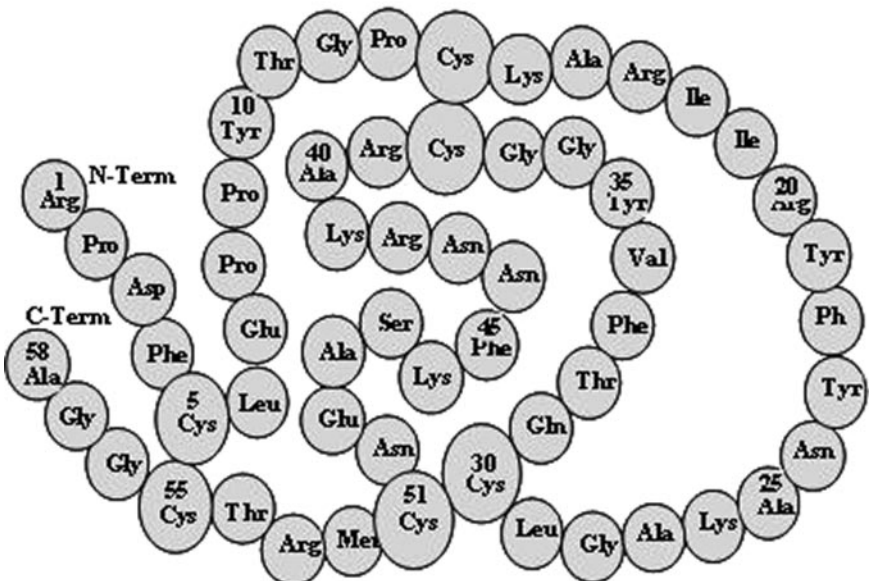


Figure 1. Molecular structures of the amino acid lysine (top left) and its analogs ϵ -aminocaproic acid (top center) and tranexamic acid (top right) and the serine protease antagonist aprotinin.



from a single center, the All India Institute of Medical Sciences.^{21–23,50,51} These studies and that published by Bulutcu et al.⁵² enrolled 750 exclusively cyanotic patients. Two studies involved EACA,^{23,51} three involved TA,^{21,50,52} and one compared both drugs.²² All six studies showed efficacy of antifibrinolytic treatment in decreasing bleeding and transfusion. Twenty-four hour blood loss was decreased 11%–44%, and treated patients received 20%–50% less blood than controls. In addition, sternal closure times were reduced 6–25 min and reexploration rates were improved by 50%–100% with antifibrinolytic therapy.

The remaining five studies included mixed groups of cyanotic and noncyanotic patients. McClure and Izsak,⁵³ studying 56 children undergoing various procedures, found an improvement in intraoperative bleeding with EACA, but postoperative bleeding was improved only in cyanotic patients. Similarly, Zonis et al.,⁵⁴ in a study of 82 patients from 1-day to 14-years-old, found no benefit of TA in the group as a whole, but decreased bleeding and transfusion requirements in a subgroup of cyanotic patients. The results of this study may have been influenced by the exclusion from data analysis of six patients who had excessive bleeding, five from the placebo group. This group subsequently performed a similar study in a group of 56 infants and children, this time also measuring various markers of hemostatic activation.⁵⁵ No benefit of TA in bleeding or transfusion was demonstrated in the group as a whole or in a subgroup of cyanotic patients. Fibrinolysis was noted to be more active in cyanotic than noncyanotic patients, as were indicators of platelet activation. These differences were measurable before surgery.

The benefit of antifibrinolytic treatment is less clear in reoperations. Williams et al.⁵⁶ performed a prospective observational case-control study of 140 patients receiving EACA or no antifibrinolytic therapy, with 132 of these patients undergoing reoperative sternotomy. Although intraoperative blood loss was decreased in the EACA group, 24 h blood loss and blood transfusion were not significantly different. Reid et al.²⁰ studied 43 children undergoing repeat sternotomy randomized to TA or placebo. Blood loss and transfusion requirements were reduced with TA using univariate analysis, but multivariate linear regression showed a difference only in bleeding. Chest closure time was decreased in the TA group using univariate analysis. A small sample size combined with a large variability in measured outcomes caused the power of this study to be low.

There may also be an effect of dose on efficacy. Chauhan et al.²¹ studied four different dosing schemes of TA versus control (Table 1). All doses studied were effective in decreasing bleeding and transfusion except the single dose of 50 mg/kg after anesthetic induction. This 50 mg/kg dose was used by both

Zonis et al.⁵⁴ and Levin et al.⁵⁵ in studies showing limited or no benefit.

Two studies evaluated the effects of lysine analogs on duration of postoperative mechanical ventilation.^{20,56} Neither study showed any benefit for this outcome, which may attest to a lack of antiinflammatory effects with these drugs.

Thus both EACA and TA appear effective in reducing bleeding and transfusion in cyanotic patients, provided an adequate dose is administered. Their efficacy in other high-risk and mixed populations is not as well established.

Aprotinin

Although early reports of the use of aprotinin during CPB provided some evidence of efficacy,^{4,57} it was not until efficacy in adults was reported⁵⁸ that prospective scientific studies followed in pediatric patients. A large body of literature has accumulated, including 14 RCTs^{6,19,23,52,59–68} (Table 2). Problems common in pediatric cardiac surgery research including heterogenous populations, small numbers of subjects resulting in low statistical power, variable CPB, surgical techniques, and surgical outcomes confound this literature. Flaws in study design are also common, as has been reported.⁶⁹ Further, there has been a large variability in dosing. In general, aprotinin-treated patients have had less blood loss and transfusion compared with controls, but the differences often have not been statistically significant (Fig. 3, Table 2).

Arnold et al.⁶⁹ attempted to combine the RCTs using meta-analysis. Although they found a combined decreased risk of transfusion in treated patients, the authors report that they were only able to use half of the available articles for the outcome of proportion of patients transfused due to the inconsistent manner in which outcomes are reported in this literature. Studies showing positive results were disproportionately represented in this analysis.

Aprotinin appears to decrease bleeding and transfusion requirements in specific circumstances. The study by Mossinger et al.⁶ in 2003 best shows the potential of aprotinin in pediatric heart surgery. Sixty patients weighing <10 kg undergoing primary corrective congenital heart surgery with CPB were enrolled in a randomized, double-blind study, including stratification by preoperative diagnosis. Aprotinin dosing was based on published pharmacokinetic data.⁷⁰ Aprotinin-treated patients had less blood loss (14 vs 20 mL/kg/24 h, $P < 0.05$) and were less likely to be transfused with red blood cells (13% vs 47%, $P < 0.05$) and cryoprecipitate (3% vs 31%, $P < 0.05$). In addition, aprotinin suppressed thrombin activation, inhibited D-dimer production, and improved postoperative PO_2/FiO_2 ratios. Mechanical ventilation time in treated patients was less than half that of controls (44 vs 101 h, $P < 0.05$). Interestingly, the authors failed to show a difference in multiple biochemical measures of the inflammatory response, including interleukin (IL)-6,

ml/kg/24 hours

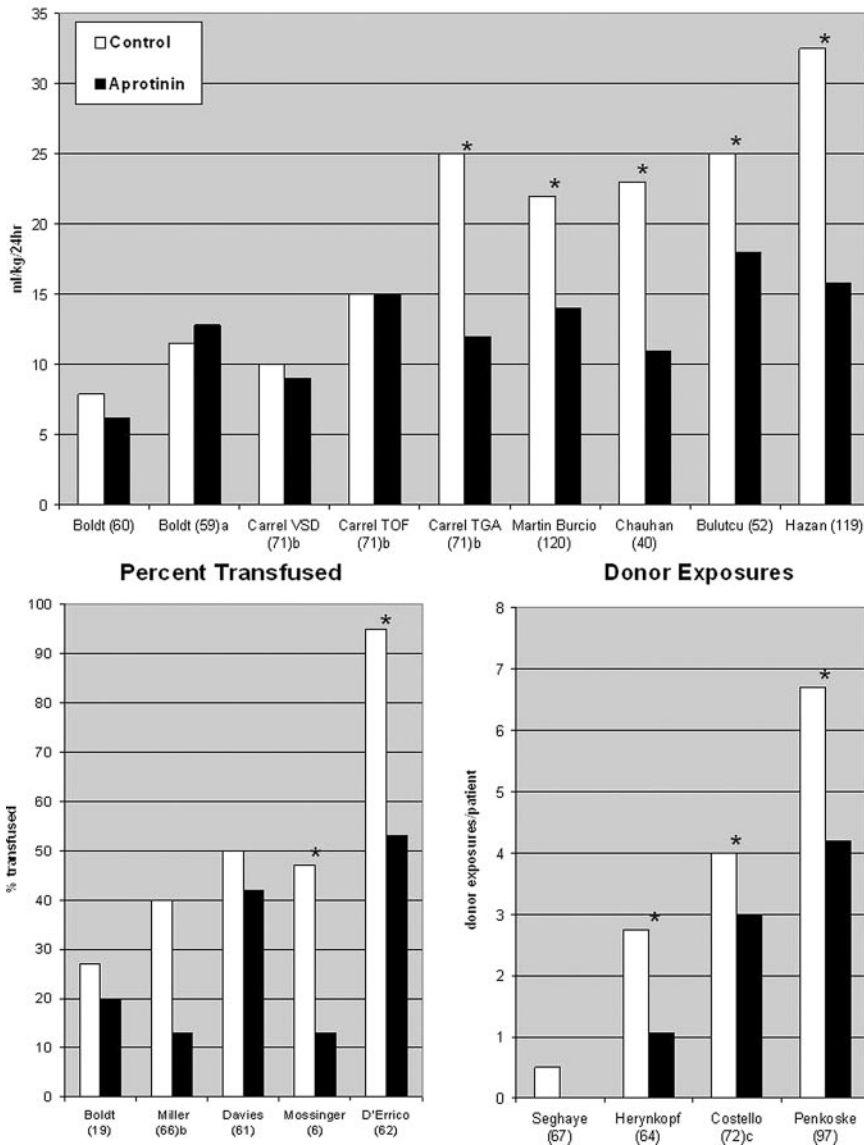


Figure 3. Reported transfusion outcomes in aprotinin studies. Transfusion is reported as: (mean) mL of red blood cells per kg for the first 24 h; percent of patients receiving red blood cell transfusion; and (median) total donor exposure. * = result significant at $P < 0.05$. a: Subgroup of patients < 10 kg, b: High-dose aprotinin versus control, c: Subgroup of repeat sternotomies, VSD = Ventricular septal defect. TOF = Tetralogy of Fallot. TGA = Transposition of the great arteries.

IL-8, and IL-10. Complement C3 was lower in treated patients only at 4 and 24 h postoperatively.

Not all studies have demonstrated a statistically significant benefit of aprotinin. Five of the 14 RCTs have shown a decrease in bleeding,^{6,23,52,63,65} and six a decrease in at least one measure of transfusion^{6,23,52,62,64,66} with aprotinin treatment. In contrast, Boldt et al.^{19,59,60} published three RCTs showing no benefit of aprotinin treatment. In one of these studies,¹⁹ 60 patients undergoing various procedures were divided into five groups: patients over 10 kg undergoing CPB with or without aprotinin, patients under 10 kg undergoing CPB with or without aprotinin, and a group undergoing major intrathoracic vascular surgery without CPB. Initiation of bypass was associated with significant changes in platelet function that were unaffected by aprotinin. In patients over 10 kg, aprotinin-treated patients had significantly increased 24-h blood loss, and treated patients both over and

under 10 kg received a larger total volume of transfused red blood cells and plasma.

One explanation of the variability in reported outcomes is that aprotinin treatment may be of benefit only in certain patients or particular operations. In adult cardiac surgery, the greatest benefit of aprotinin treatment is observed in patients at high risk of bleeding, and this is reflected in the current package insert.⁴⁴ The published RCTs of aprotinin in the pediatric population, however, have all involved infants and older children with a wide variety of diagnoses, both cyanotic and noncyanotic. Neonates, reoperations, complex and simple operations are represented in variable proportion. Presumably, there is a significant variability of risk for bleeding and transfusion in such a mixed population.

Two studies have attempted to discern whether aprotinin might be of benefit in specific types of surgery. Davies et al.⁶¹ randomized 42 infants and

Table 3. Observational Studies of Aprotinin versus Placebo

Study	Year	N	Age	Bleed	Trans	Other	Load (KIU/kg)	Infusion (KIU/kg/h)	Prime (KIU/kg)
Hazan ¹¹⁹	1991	20	7.3 yr	+	+		30,000	1 × 10 ⁵ KIU/hr	10 ⁶ KIU
Ranucci ⁹⁸	1994	30	15 d–6 yr	–	NR	PV(–)	0 (prime only)	0	30,000
Penkoske ⁹⁷	1995	80	5.9 ± 5 yr	+	+	CT(+); RE(–)	28,000	7000	28,000
Carrel ⁷¹	1998	168	4 d–15 mo	–	–		0	0	500,000 KIU
				+ ^a	+ ^a		50,000	20,000	50,000
Martin-Burcio ¹²⁰	2001	71		+	+		1.7 × 10 ⁶ /M ²	4 × 10 ⁵ /M ²	1.7 × 10 ⁶ /M ²
Costello ⁷²	2003	112	1 d–6.4 mo	–	(+) ^b	CT, PV(+); RE(–)	1.7 × 10 ⁶ /M ²	4 × 10 ⁵ /M ²	1.7 × 10 ⁶ /M ²

Age is given as range or mean ± standard deviation.

Bleed = blood loss at 24 hours; Trans = transfusion of red blood cells and/or products; + = treated patients showed benefit relative to controls; – = no benefit was shown; NR = not reported; Other is other reported outcomes including: time required for chest closure (CT), incidence of reoperation for bleeding (RE); PV = Postoperative ventilation time (PV); KIU = kallikrein inhibiting units.

^a Decreased bleeding and transfusion was found only in a subgroup of patients having complex neonatal surgery and receiving high-dose aprotinin.

^b Transfusion was less only in subgroup of repeat sternotomy patients.

children to receive aprotinin or placebo. Randomization was stratified by type of surgery into three groups: infants undergoing “major open heart” surgery with deep hypothermia (<22°C) and low-flow (<1.3 L/min/m²) CPB, children aged between 1 and 5 years having “major reconstructive surgery” [e.g., tetralogy of Fallot (TOF) repair or Fontan], and children over 1 year of age having reoperative surgery. There was no effect of aprotinin in the entire study population, nor in any specific category. The numbers in each treatment group were very small, limiting power. In the Mossinger et al.⁶ study detailed above, randomization was stratified by diagnosis [complete atrioventricular septal defect, transposition of the great arteries (TGA), TOF, ventricular septal defect (VSD)]. Although there was evidence of treatment benefit in the entire study population, there did not appear to be greater or lesser benefit in any particular diagnosis, although again the subgroups were small.

In a prospective, observational study, Carrel et al.⁷¹ enrolled 168 children <15 kg who were undergoing repair of VSD, TOF, or TGA. The patients received high-dose or low-dose aprotinin (Table 3) or no anti-fibrinolytic treatment. TGA patients receiving high-dose aprotinin had less bleeding than low-dose or control patients. TGA patients also had a dose-dependent decrease in fibrinolysis with aprotinin treatment; production of fibrin split products and D-dimers were both inhibited by aprotinin in a dose-dependent fashion. There was no benefit of aprotinin in VSD or TOF patients.

Patients undergoing repeat cardiac surgery are at increased risk for postoperative bleeding. Miller et al.⁶⁶ studied 45 infants and children undergoing repeat sternotomy for various indications, 40% having Glenn shunts or Fontan surgery. Patients were randomized to receive high-dose or low-dose aprotinin, or no treatment. Although there was no difference in bleeding between groups, fewer patients receiving high-dose aprotinin required transfusion of plasma and platelets in the operating room and chest closure time was also shorter in this group. Transfusion of red

blood cells was not different between groups, nor was transfusion of any blood product in the intensive care unit. Costello et al.⁷² published a retrospective study of 36 infants and children undergoing cardiac surgery with CPB using historical controls. Aprotinin-treated patients had decreased sternal closure times, but only the subgroup of repeat sternotomies had a significant decrease in red cell and plasma donor exposures.

One factor that may influence the differences in reported outcomes is the variability in the doses of aprotinin reported in the literature. Five studies have specifically investigated the effect of dose, comparing two different dosing schemes with control.^{59,62,63,66,71} Dietrich et al.⁶³ randomized 60 patients under 10 kg to high or low dose aprotinin (Table 2) or no treatment. The high-dose group had less chest tube output at 6 h postoperatively as well as a decrease in thrombin activation and fibrinolysis relative to low-dose and control. An inverse correlation was also found between the plasma concentration of aprotinin at the end of bypass and the degree of thrombin activation ($r^2 = 0.18$, significance not stated), i.e., higher aprotinin concentration appeared to better inhibit contact activation of coagulation. Similarly, Miller et al.⁶⁶ (Table 2) and Carrel et al.⁷¹ (Table 3) in their previously discussed studies, found aprotinin effective only in the high-dose groups. Boldt et al.⁵⁹ studied 42 patients <20 kg randomized to control or two doses of aprotinin (Table 2) slightly smaller than those used by Dietrich et al.⁶³ Although there was no benefit of either aprotinin dose on blood loss, transfusion or platelet function, the low dose aprotinin group received more plasma transfusion than either the high-dose group or controls. D’Errico et al.⁶² randomized 61 children with various diagnoses to high or low dose (Table 2) aprotinin or placebo. Although blood loss was not significantly different, both aprotinin groups received fewer transfusions of red blood cells, platelets, and plasma, and had fewer total donor exposures.

Despite the demonstrable effect of dose, this alone cannot explain the presence or absence of efficacy. Chauhan et al.²³ were able to demonstrate that a low

dose can decrease bleeding and transfusion of red blood cells, plasma, and platelets, whereas Davies et al.⁶¹ found a much larger dose (Table 2) was not effective in reducing bleeding or transfusion, despite a reasonably similar group of subjects.

Center-specific practices may also alter aprotinin's effectiveness. The German Heart Center in Munich has consistently demonstrated the drug is effective,^{6,63,70} while across Germany in Giessen, Boldt's group has repeatedly demonstrated that it is not.^{19,59,73} It is unclear whether the conduct of CPB, anticoagulation, transfusion, or surgical technique is more important in efficacy differences between centers.

Two studies have demonstrated other potential benefits of aprotinin in congenital heart surgery. In a RCT from 1999, Wippermann et al.⁶⁸ showed a modest decrease in the requirement for inotropic support in patients randomized to receive aprotinin relative to a placebo group. The group was unable to show differences in other measures of ventricular function, but the results are consistent with previously published basic⁷⁴ and clinical⁷⁵ studies showing a protective effect of aprotinin against ischemia-induced myocardial dysfunction. In a retrospective study published in 1996,⁷⁶ Tweddell et al. found a decrease in transpulmonary pressure gradients in aprotinin-treated patients after bidirectional Glenn or Fontan procedures. This effect may be of significant benefit in the large number of pediatric cardiac patients at risk for pulmonary hypertension. These clinical benefits may be related to the antiinflammatory effects of aprotinin, which have been repeatedly demonstrated in adults.^{48,49}

Safety

Lysine Analogs

Studies investigating the effects of lysine analog and aprotinin in congenital cardiac surgery do not have sufficient power to determine safety. Theoretically, the primary serious risk of the lysine analogs is thrombosis. None of the prospective studies of efficacy has documented any increased risk of complications due to antifibrinolytic therapy. There are case reports of severe thrombotic complications in patients treated with antifibrinolytics, including a case of fatal aortic thrombosis in a neonate on extracorporeal membrane oxygenation.⁷⁷ A single retrospective study of 71 patients having modified Fontan procedures found no increase in baffle fenestration closures with antifibrinolytic treatment, but it was underpowered.⁷⁸ In study of 431 extracorporeal membrane oxygenation patients reported by Downard et al. in 2003,⁷⁹ circuit changes were more frequent in EACA-treated patients, but whether this was due to increased thrombus formation or institutional practice is not known. Much larger numbers of subjects will have to be studied in order to assess the relative likelihood of various infrequent or rare adverse events related to the use of TA and EACA, such as thrombosis, renal

failure, myocardial infarction, stroke or death. Such safety studies are unlikely to be performed, given that these are generic products, and the manufacturers have little incentive to sponsor such investigations. EACA is capable of producing a proximal skeletal muscle myopathy which has been described in pediatric patients.⁸⁰ Rapid IV injection of TA or EACA may cause hypotension which may be attenuated by slow infusion; the manufacturer recommends the initial loading dose be given over 1 h.³⁸

Aprotinin

Before obtaining FDA approval for aprotinin, Bayer acquired a large safety database in adult patients undergoing CABG. There is no such database for the use of aprotinin in pediatric patients, and no study appropriately powered to find significant differences in rare adverse outcomes has been performed. Of the multiple randomized studies discussed, none has sufficient power to evaluate safety, and only one provides information on adverse events in any detail.⁶¹ No difference in complication rates was reported in any prospective study. Most concerns about the safety of aprotinin relate to one of three areas: thrombosis, renal effects, and anaphylaxis.

Thrombosis

Concerns arose about the potential for aprotinin to create a prothrombotic state in adults beginning with a publication by Cosgrove et al.⁸¹ in 1992 reporting thrombosis in vein grafts of coronary bypass patients. Subsequent well designed prospective studies^{82,83} did not find any additional risk of graft thrombosis until the IMAGE trial published in 1998⁸⁴ in which aprotinin-treated adult coronary patients had an increased risk of coronary graft thrombosis relative to placebo. Careful analysis of their data showed that this increased risk could be attributed to patients from a single center. Taken together, this evidence would suggest that under most circumstances aprotinin does not increase the risk of graft thrombosis, but it may do so under some poorly understood circumstances. There is also evidence that aprotinin has antithrombotic properties in adults due to inhibition of the generation of thrombin⁴⁶ and inhibition of platelet activation⁸⁵ during CPB.

Infants and children undergoing cardiac surgery are at high risk for postoperative thrombosis.⁸⁶ Small vessel size, prolonged immobility, artificial shunts of thrombogenic material, low flow states, central catheters, and high blood viscosity may all contribute to a prothrombotic state. Indeed the incidence of central line-associated thrombosis in pediatric cardiac surgery patients has been reported to be as high as 20%.⁸⁷ Published evidence concerning the potential for thrombotic risk with aprotinin in pediatric heart surgery is limited. Although there are case reports documenting thrombosis in aprotinin-treated patients,^{88,89} it is not clear what role aprotinin played in the genesis

of the complication. In the largest single review of pediatric experience with aprotinin, Jaquiss et al.⁹⁰ found no increased risk of thrombosis in 865 aprotinin exposures.

Although there is no published evidence that aprotinin increases thrombosis in these patients, multiple factors including transfusions may affect thrombosis in patients. Aprotinin has complicated effects on the coagulation system, which result in both an anticoagulant effect demonstrable with the activated clotting time⁹¹ and the activated partial thromboplastin time,⁹² and better preservation of the hemostatic system.⁴⁹ Although under ordinary conditions fibrinolysis is not necessary to maintain the fluidity of blood, fibrinolysis may be critical in neonates during and after CPB, since neonates may lack sufficient intrinsic cofactors for heparin to be fully effective in inhibiting intravascular thrombin generation.^{93,94} Additionally, cyanotic patients may have continuing activation of coagulation and fibrinolysis before surgery.⁵⁵ The question of thrombotic risk with aprotinin in pediatric patients can be answered only by a large randomized trial.

Renal Effects

Aprotinin is taken up by the brush border of the renal tubules after filtration.⁹⁵ This has led to concerns about the potential for renal toxicity. Questions about renal toxicity in adults have been raised by two observational studies. In a prospective, multicenter, observational study of 4374 CABG patients,²⁹ Mangano et al. found a two-fold increase in renal dysfunction or dialysis in both complex and primary coronary surgery. Renal dysfunction was defined as a creatinine increase to at least 177 $\mu\text{mol/L}$ with an increase of at least 62 $\mu\text{mol/L}$. Several issues challenge the conclusions of this study, including what the comorbidities were in their multifactorial analysis, failure to control for the effect of treatment center, and the role of transfusions in outcomes. In the report, fresh frozen plasma administration carries the same risk for renal failure as aprotinin (Odds ratio 2.4 vs 2.41). The second study was a retrospective, propensity-score matched case-control study of 898 patients undergoing cardiac surgery and treated with aprotinin or TA at a single center.²⁸ Karkouti et al.²⁸ found a significant increase in renal dysfunction (defined by creatinine increase of more than 50% or need for dialysis) in those receiving aprotinin. Previous reports note that aprotinin is capable of producing transient increases in biochemical markers of renal dysfunction. Prospective, RCTs of aprotinin in adult cardiac surgery have not shown an increase in renal failure requiring dialysis in treated patients.^{82,83,96}

Eight studies investigating aprotinin in pediatric patients have reported renal outcomes, with half finding no differences in postoperative creatinine between aprotinin-treated patients and controls.^{6,61,76,97} In a retrospective matched case-controlled study of 30 patients who had undergone congenital heart surgery

with CPB,⁹⁸ Ranucci et al. showed a moderate increase in serum creatinine on the first postoperative day in aprotinin-treated patients but did not report resolution or progression to renal failure. Seghaye et al.⁶⁷ found no difference between treated and control patients in postoperative creatinine clearance in their prospective randomized study. In the RCT reported by D'Errico et al. in 1996,⁶² control patients had a transient increase in postoperative blood urea nitrogen that was not seen in aprotinin-treated groups. The low-dose aprotinin group had a transient decrease in creatinine not seen in the high-dose or placebo groups. Similarly, in a study by Miller et al. from 1998,⁶⁶ placebo group patients had a transient increase in creatinine on arrival in the intensive care unit that was not seen in aprotinin-treated patients. Although the weight of published evidence would suggest there is no increased risk of renal failure with aprotinin treatment in congenital heart surgery, the power of these small studies to discern even a two-fold increase in this complication is small, and no clear conclusion can be reached.

In September, 2006, an FDA Advisory Committee reviewed available published data, including the Mangano et al. and Karkouti et al. articles, and concluded that the weight of evidence supported the safety of aprotinin in its approved indication. They recommended restricting its use to cases where there is a clearly increased risk of bleeding⁹⁹ and strengthened the package insert warnings regarding the risk of anaphylaxis. Meeting in September, 2007, the FDA Advisory Committee again voted to leave aprotinin on the market, but recommended the manufacturer perform new safety research (<http://www.fda.gov/ohrms/dockets/ac/07/minutes/2007-4316m1.pdf>. Last accessed 10/9/07).

Anaphylaxis

Aprotinin, a protein derived from bovine lung, has significant antigenic potential, and fatal anaphylactic reactions in adults have been reported.¹⁰⁰ In a review of 121 cases (46 children) of aprotinin reexposure from the German Heart Center in Munich, 12% of patients developed high titers of antiaprotinin immunoglobulin (Ig)G within a week of receiving the drug.¹⁰¹ A high titer antiaprotinin IgG before exposure had a 100% sensitivity and a 98% specificity for a subsequent anaphylactic reaction. From the same center, another study of 248 aprotinin reexposures, including 147 pediatric cases, found an overall reaction rate of 2.8%, including mild and moderate reactions of uncertain relationship to aprotinin.¹⁰² Five of the seven reactions occurred in patients who were reexposed to aprotinin within 6 months of a prior dose, which led to initial recommendations that the drug not be given within 6 months of a prior exposure. The current FDA recommendation is to avoid use of aprotinin within 12 months of a prior exposure.⁴⁴ The review of an additional year of data from the German Heart Center

provided a total of 254 reexposures in pediatric patients,¹⁰³ with 1.2% (3/254) suffering reactions, less than half the adult rate of 2.7% (5/183) ($P = 0.27$). In 2002, Jaquiss et al.⁹⁰ examined 865 pediatric aprotinin exposures, 681 of which were primary. They found an overall reaction rate of 1.16%, with a rate of 1.6% in reexposures, which was not significantly different from that for primary exposures. Most recently, the German Heart Center reported the largest published aprotinin experience: 12,403 exposures including 2769 pediatric patients.¹⁰⁰ They found that 6 of 453 pediatric patients (1.3%) reexposed to aprotinin had reactions, while only 1 of 2202 primary exposures (0.05%) experienced a reaction. Similar rates were found in adults: 1.7% for reexposures and 0.1% for primary exposures. Interestingly, the group reported a complete absence of severe reactions after 1998, which the authors attribute to improved screening for patients at risk for reexposure, more careful administration of aprotinin in reexposures, and elimination of aprotinin use in recently exposed patients.

A possible explanation for a lower incidence of aprotinin reactions in pediatric patients is that the immune system of neonates is immature.¹⁰⁴ Neonates secrete significantly less immunoglobulin, and do so in a delayed fashion relative to adults.¹⁰⁵ This is particularly true for IgG, and is due to immaturity of both T- and B-cell function.¹⁰⁶ Since neonates are approximately one-fifth of pediatric cardiac surgery patients (STS database, 1998–2002), they are a large group that not only is unlikely to have a reaction with primary exposure, but is also unlikely to be sensitized and thus have a reaction on subsequent exposure. Pediatric patients who do have an aprotinin reaction may also be more likely to survive it. Although a review of 124 hypersensitivity reactions to aprotinin¹⁰⁷ found an overall mortality of 9%, deaths occurred only in adults. Twenty pediatric aprotinin reactions have been reported and all these patients have survived without permanent deficit.^{90,101,102,108–112}

Measures to avoid anaphylactic reactions have been ineffective. Skin testing has a poor predictive value, and anaphylactic reactions have been reported with even this small exposure.⁹⁰ An IV test dose of 1 mL (10,000 KIU) for adult dosing is recommended and used in pediatric applications.¹⁰³ However, this test dose has proved to be neither predictive nor safer than the initial loading dose, i.e., patients have had anaphylactic reactions to the initial dose after a negative test dose, and the test dose itself has provoked anaphylactic reactions.¹⁰² Antibody testing may have some promise, however the low incidence of reactions results in a positive predictive value for high-titer IgG of only 60%.¹⁰¹ In addition, there is no antiaprotinin antibody test available in the United States. Pre-treatment with antihistamines and/or steroids is not effective in eliminating reactions, although there are insufficient data to draw conclusions about potential benefit in decreasing their severity.¹⁰² The

current package insert recommends that the test dose and initial loading dose not be administered until there are conditions for rapid cannulation and initiation of CPB.⁴⁴

Comparisons and Combinations

With the considerable variability among studies of the three drugs under consideration in terms of design, dose, and outcomes, it is difficult to draw any conclusions about relative efficacy from the literature. There are a few published comparison studies. In 2000, Chauhan et al.²³ published a study comparing low-dose aprotinin, EACA and the combination in 300 cyanotic patients having cardiac surgery (Tables 1 and 2). There was no difference between EACA-treated and aprotinin-treated patients in any measured variable: 24-h blood loss, transfusion, reexploration, or coagulation tests. A combination of the two drugs was more effective than aprotinin in decreasing reexploration risk, but otherwise there was no difference in any variable between the combination and either drug alone. Subsequently, the same group compared TA and EACA in a placebo-controlled study of 150 patients with cyanotic CHD aged 2 months to 14.5 years.²² Both drugs were superior to placebo, but there were no significant differences between the treated groups with respect to 24-h blood loss, transfusion or reexploration rate. The final comparison, aprotinin and TA, was published by Bulutcu et al. in 2005.⁵² One-hundred children were evenly divided into four groups: placebo, TA, aprotinin, and a combination of the two drugs. Again, all treatment groups fared better than placebo in 24-h blood loss and transfusion, with no significant differences among the three treated groups. Thus the limited comparative evidence would suggest that the three drugs are equivalent in efficacy for reduction of bleeding and transfusion, at least with the doses and patients studied, and there is little or no advantage to combination therapy.

Despite the lack of therapeutic benefit, there is some synergy between lysine analogs and aprotinin in plasmin inhibition,¹¹³ as the two classes of drugs inhibit fibrinolysis in a slightly different manner. This synergism may explain the observation that administration of the combination of EACA and aprotinin in a swine model produces diffuse microvascular thrombosis.¹¹⁴

Dose

One of the most notable points in a review of this literature is the wide variation in doses of all three drugs. Including only prospective RCTs, in 14 aprotinin studies, 14 different doses were used. For EACA, four studies used two different dosing schemes, and in seven TA studies, six doses were investigated. Ideally, drug doses should be determined with an understanding of the pharmacodynamics and pharmacokinetics of the drug in the population of patients being treated. Initially, dosing schemes for TA, EACA and aprotinin

were based on extrapolations of established adult schemes, but we have since accumulated enough pharmacokinetic information to make more sensible dosing decisions.

Because EACA and TA are not indicated for use in CPB, there have been no industry-sponsored trials to establish pharmacologically based doses for pediatric heart surgery. Therefore, dosing schemes have been chosen empirically. Many regimens used clinically or studied have included a pump priming dose equivalent to the initial loading dose, as in the Hammersmith aprotinin regimen. There is no pharmacokinetic basis for this relationship, as the CPB kinetics of the two classes of drugs are quite different.

The pharmacokinetics of EACA in children undergoing CPB have been studied in eight patients aged 9 months to 4 years.¹¹⁵ A dosing scheme using three boluses of 50 mg/kg was used, and concentrations were measured at several time points. Based on derived kinetics, the authors proposed an initial loading dose of 75 mg/kg, a pump priming dose of 75 mg/kg with an infusion of 75 mg/kg/h to establish and maintain a therapeutic plasma concentration [130 mcg/mL]¹¹⁶ in 95% of patients. No rationale was provided for dosing the fixed volume of the pump prime based on the patient's weight.

The pharmacokinetics of TA in children undergoing CPB have been estimated using adult EACA data,¹¹⁷ together with the relative pharmacokinetics of EACA in adults and children.¹¹⁸ Two published dosing schemes were modeled, those reported by Zonis et al.⁵⁴ and Reid et al.²⁰ (Table 1). Modeling of the Zonis et al. dosing scheme (50 mg/kg load only) showed that serum TA concentrations would decrease below the assumed therapeutic level (20 mcg/mL) during CPB, perhaps explaining the relative lack of efficacy found in that study. In contrast, the dose used by Reid et al. produced levels well in excess of the therapeutic range. Unfortunately, the authors did not suggest a pharmacokinetics-based dosing scheme. Chauhan et al., in a dose-ranging study of TA published in 2004,²¹ found the most effective dosing scheme of the four he studied to be a 10 mg/kg load, 10 mg/kg in the pump prime and 10 mg/kg after protamine. Although this scheme may not make pharmacokinetic sense, it has shown clinical efficacy.

Adult dosing of aprotinin was originally developed to produce plasma levels adequate for kallikrein inhibition. Kallikrein had been found to be inhibited at an aprotinin concentration of 200 KIU/mL.⁴⁸ Clinical investigation determined that an initial loading dose of 2×10^6 KIU, followed by an infusion of 5×10^5 KIU/h established and maintained a therapeutic concentration.⁴⁸ Addition of 2×10^6 KIU to the pump prime was found to be necessary to avoid a dilutional decrease in this concentration.⁴⁸ Pediatric doses were extrapolated

from this regimen. It was correctly surmised that adjustment of the initial loading dose should be based on weight or body surface area.¹¹⁹ The pump priming dose has been mistakenly calculated on the same basis, despite the obvious large difference in the relationship between blood volume and pump prime in pediatric (especially neonatal) and adult patients. Use of weight-based pump-prime doses produces low, presumably ineffective levels in small patients (primarily neonates) and unnecessarily high concentrations in larger patients. This was recognized and described by Deitrich et al. in 1993,⁶³ and again by Oliver et al. in 2004.¹¹⁹ Mossinger and Dietrich reported the success of a pharmacokinetics-based dose of 30,000 KIU/kg load and a fixed 500,000 KIU in the pump prime in establishing a therapeutic level during CPB in patients under 10 kg.⁷⁰ This concentration was maintained throughout CPB, despite the absence of a continuous infusion. This group prospectively evaluated this scheme in 30 infants,⁶ and in contrast to their prior data, although initial CPB concentrations were adequate, there was a steady decline in aprotinin concentrations during CPB in the absence of a continuous infusion. Oliver et al.¹¹⁹ evaluated a slightly different scheme in 30 patients of various ages at the Mayo Clinic, using an initial loading dose of 25,000 KIU/kg and an infusion of 12,500 KIU/kg/h, with a pump prime dose of 35,000 KIU/kg. This was effective in patients over 10 kg, but smaller patients did not achieve therapeutic concentrations during CPB due to the greater hemodilution of a weight-based priming dose in small infants. Together, these data suggest that a continuous infusion is necessary; an initial loading dose should be at least 30,000 KIU/kg, and the pump-prime dose should be based on the volume of the pump, rather than the weight of the patient.

CONCLUSIONS

Evidence supports the efficacy of the lysine analog antifibrinolytics and aprotinin to decrease bleeding and transfusion in pediatric patients undergoing cardiac surgery involving CPB. This benefit is likely to be more significant in certain high risk groups, such as cyanotic patients, complex surgery and reoperations. The limited available evidence suggests that there is no difference in efficacy between the lysine analogs and aprotinin. Care must be taken to assure that the dosing scheme for these drugs will result in effective plasma concentration during CPB. The available published literature is inadequate to evaluate the safety of these drugs in this setting. The large number of small studies showing no excess risk in treated patients versus placebo-treated controls suggests that there is not a large risk involved with antifibrinolytic therapy in the pediatric population, but this is hardly definitive. None of these drugs has a FDA indication for pediatric cardiac surgery. Further research should be directed toward establishing the safety of the two

classes of drugs in pediatric heart surgery, their relative efficacy, and efficacy in particular types of patients (e.g., neonate versus older, cyanotic versus noncyanotic). Effective dosing schemes need to be clarified, especially in neonates, and the potential benefits of the antiinflammatory effects of aprotinin elucidated.

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