*Paediatric and Perinatal Drug Therapy, 2004; 6 (1)*

# The use of antifibrinolytic drugs in paediatric cardiac surgery

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**Cardiopulmonary bypass (CPB) activates coagulation, inflammatory and fibrinolytic systems due to exposure of the patient's blood to the bypass circuit. This response tends to be worse in children than adults. Antifibrinolytic drugs (aprotinin, tranexamic acid, epsilon aminocaproic acid) are used to decrease blood loss, but data about indication, pharmacokinetics, dose and effectiveness for some of these drugs remains sparse and contradictory. Lysine analogues, such as tranexamic acid and epsilon aminocaproic acid (EACA) act by blocking the lysine binding site on plasminogen. Aprotinin is a nonspecific serine protease inhibitor. Serine proteases are involved in the coagulation, fibrinolytic and complement cascades. Aprotinin may have potential benefits beyond blood loss reduction and may have beneficial effects not directly related to antifibrinolysis. Clearance of aprotinin and tranexamic acid is renal and the kidney is immature in infancy. The influence of hypothermia, the systemic inflammatory response, CPB circuitry and relative prime volumes are missing from paediatric analyses. Paediatric cardiac operations are mostly for congenital disorders and may be associated with other organ dysfunction, reduced growth, poor nutritional status and bleeding diathesis. Pharmacodynamics may also be altered in infancy because the coagulation cascade is immature. The effects of concomitant drug therapy that may also effect coagulation are unknown. The lack of clinical effect measures that can be used to describe concentration-response data has lead to the use of target concentrations determined from *in vitro* studies that may not be applicable *in vivo*. Risk-benefit analyses (*e.g.* thrombotic events *vs* reduced blood loss) have not been made for children undergoing cardiac surgery.**

Paed Perinatal Drug Ther 2004; 6: 4–13

*Keywords:* Antifibrinolysis – paediatric – cardiac surgery

## Introduction

Cardiopulmonary bypass (CPB) activates coagulation, inflammatory and fibrinolytic systems due to exposure of the patient's blood to the bypass circuit. In children, this exposure and the relative contribution of the CPB circuit prime to total circulating volume are greater than in adults. Coagulopathy related to CPB, contributed to by dilution, consumption of clotting factors, fibrinolysis and platelet dysfunction, tends to be worse in children than adults. Relative blood loss

and allogenic blood and blood product requirements are greater in children undergoing open heart surgery than adults. Blood loss in paediatric cardiac surgery with CPB has been reported to range from 15 to 110 ml/kg[1]. Strategies to minimise blood loss include changes in surgical technique and CPB circuit technology, administration of blood products, cell saving and pharmacological interventions. Antifibrinolytic drugs are the most commonly employed pharmacological strategy.

Antifibrinolytic drugs (aprotinin, tranexamic acid, epsilon aminocaproic acid, desmopressin) are now routinely used in many institutions to decrease blood loss, but data about indication, dose and effectiveness for some of these drugs remains sparse and contradictory[2], even in adults[3]. Optimum duration of treatment is unclear. Haemostatic derangement continues after CPB and the role of continued antifibrinolytics during this period is uncertain[3]. Some adult dosing schedules are based on doses previously determined to inhibit plasma fibrinolytic activity in settings outside cardiac surgery, while others were developed empirically[4,5]. Rationalisation of adult dosing has occurred over the last few years[4,6]. Paediatric doses are often extrapolated from adult dosing regimens without supporting pharmacokinetic or pharmacodynamic data from children undergoing CPB.

## Coagulation system in children

Children less than 8 kg can be expected to have more severe coagulopathies, require more coagulation product transfusions and bleed more after cardiopulmonary bypass[7]. Infants have decreased levels of factors II, V, VII, X, XI and XII until 6 months of age[8,9]. The prothrombin time (PT) is normal, but the activated partial thromboplastin time (APPT) is prolonged at birth and reaches adult values by 3 months of age[8]. It is postulated that poor perfusion due to the cardiac disease in infants less than 3 months of age may further delay hepatic maturation. Children with cardiac disease weighing less than 10 kg have reduced preoperative platelet aggregation as measured by adenosine diphosphate, collagen and epinephrine induced aggregation[10]. Children with cyanotic heart disease have thrombocytopenia inversely related to arterial haemoglobin oxygen saturation[11], impaired adenosine diphosphate induced platelet aggregation[12] and chronic disseminated intravascular coagulation[13]. Decreased concentrations of high molecular weight multimers of von Willebrand factor (vWF) have been reported in children with non-cyanotic heart disease[14].

Infants without congenital heart disease, although having measurable differences in their coagulation factors compared to adults, do not appear to have a clinical coagulopathy during non-cardiac surgery. Thrombelastography (TEG), a test providing a functional evaluation of coagulation, was used to assess the haemostatic system of 237 healthy paediatric patients, less than 2 years of age, undergoing elective non-cardiac surgery. TEG revealed no defects in coagulation in relation to age, indicating a functionally intact haemostatic process even in neonates. Indeed, children less than 12 months of age were found to initiate and develop clot faster than adults, with the coagulation process slowing to adult rates after 1 year of age[15].

## Effect of CPB on coagulation

Both the coagulation and fibrinolytic systems are activated during CPB[16-18]. The interaction between blood and the synthetic surfaces of the heart-lung machine activates plasma protein systems and blood cells to produce a host of vasoactive substances that mediate the "whole body inflammatory response" associated with CPB[19]. Factor XII, activated by exposure to the non-endothelial surfaces of the CPB circuit, is cleaved into two serine proteases activating both the coagulation and complement cascades. Platelets are activated to aggregate, adhere to adsorbed fibrinogen, and release granule contents. Complement stimulates neutrophils to adhere to the walls of blood vessels and release vasoactive and cytotoxic substances. Endothelial cells produce tissue plasminogen activator, which generates plasmin, a fibrinolytic enzyme, from plasminogen. Capillary permeability increases, fluid is lost from the intravascular space, and generalised oedema and inflammation impair the function of essentially every organ[19].

Heparin is administered to inhibit the formation of fibrin, but is involved in other parts of the coagulation and inflammatory cascades as well. Thrombin already bound to fibrin is less accessible to heparin, so fibrin formation and polymerisation take place despite heparin treatment during CPB. It is theoretically possible that the faster activation of clotting in infants detected by TEG described above[15] could be a disadvantage when coagulation is activated by CPB, increasing the consumption of coagulation factors.

The inflammatory response to CPB is more profound in the paediatric population compared to adults, manifested by increased complement degradation products, heightened pulmonary vascular activity, and coagulopathy[20]. Thromboxane concentration, used as a marker of the inflammatory response, is inversely related to age[20].

Dilutional coagulopathy due to CPB is more marked in children. The relatively large priming volume of the CPB circuit compared to blood volume may cause as much as 50% dilution of factors I, II, V, VII, IX and X[21]. The platelet count may decrease by as much as 70%, attributable to both dilution and adherence to the circuit[21]. Antithrombin III concentrations are diluted more than in adults, contributing to a relative heparin resistance[21].

Weight and duration of CPB are predictors of post-CPB chest tube drainage in children. Analysis of weight showed 8 kg to be a critical weight, below which post-CPB coagulopathies should be expected to be more severe, 24-hour chest tube drainage higher, and transfusion requirements greater[7]. Fibrinolysis occurs during CPB in infants[16], but the impact of this fibrinolysis may not be as important in infants and young children as in adults[22].

## Monitoring of the fibrinolytic system and efficacy of antifibrinolytic drugs

*Blood loss*

In cardiac surgery involving CPB, the primary clinical indication for perioperative administration of an antifibrinolytic drug is to decrease blood loss. Clinically, and in trials assessing antifibrinolytic drugs, measurement of blood loss has usually been the main endpoint. Although intuitively attractive, this may be a "surrogate" endpoint in small children, especially when usual blood loss is modest, as changes in absolute blood loss may have little bearing on blood product requirement and outcome, especially if blood from the CPB circuit can be re-transfused after CPB.

The mechanism of action of antifibrinolytic drugs varies. For example, tranexamic acid is a specific inhibitor of plasmin interaction with fibrin whereas aprotinin inhibits, not only plasmin, but other serine proteases, producing wide ranging effects including a direct platelet protective effect and attenuating the contact phase of coagulation through kallikrein inhibition[16]. Aprotinin's affect on blood loss may not all be due to antifibrinolysis, and potential benefits of aprotinin may not be limited to decreasing blood loss, as anti-inflammatory actions, such as inhibition of complement activation, may have clinical benefits.

*Markers of coagulation, fibrinolysis and inflammation*

The different mechanisms of action of antifibrinolytic drugs have led to the use of markers of coagulation, fibrinolysis and the inflammatory process to monitor effect. Coagulation may be assessed by serum fibrinogen concentration, platelet count, APPT, kaolin activated clotting time (ACT) and prothrombin ratio. The split products of cross-linked fibrin, degradation products of fibrinogen, the complex of thrombin with antithrombin III, F1/F2 prothrombin fragments, elastase in complex with α1-protease inhibitor and fibrin monomers have all been used to estimate thrombin activation. Fibrinolytic activation and blood euglobulin fraction have been estimated by the use of plasminogen containing human fibrin plates. The development of a lysis area indicates extrinsic plasminogen activator in the sample[16]. The inflammatory response has been assessed by the use of inflammatory markers (interleukin: IL-6, IL-8, IL-10), C-reactive protein (CRP) and complement activation (C3a)[3]. Platelet function has also been assessed by plasma thromboxane $B_2$, markers of α-granule or dense granule content of adenosine diphosphate, and flow cytometry[23]. These measurements help elucidate the effects of antifibrinolytic drugs, but can be considered "surrogate outcomes", not necessarily linked with clinical outcome.

*A target concentration based on* in vitro *studies*

Antifibrinolytic drug serum target concentrations *in vivo* remain undefined. Consequently some authors have given doses that achieve an antifibrinolytic target concentration based on *in vitro* studies[6]. A plasma tranexamic acid concentration known to reduce tissue plasminogen activator activity by 80% *in vitro* is 10 mcg/ml[24]. This is a concentration sufficient to suppress fibrinolytic activity. Tranexamic acid may also abolish plasmin-induced platelet activation *in vitro* at 16 mcg/ml[25]. Examining the conflicting results produced by different *in vitro* tests of this action highlights the hazards of extrapolating to *in vivo* conditions. Tranexamic acid inhibition of plasmin-induced platelet activation using normal human platelet rich plasma and porcine plasmin revealed a 13-fold lower concentration of tranexamic acid for 50% inhibition when plasmin was preincubated with the drug (1.2 mcg/ml, 95% CI = 1.13–1.60 mcg/ml) compared to when platelet rich plasma was preincubated with the drug (16 mcg/ml, 95% CI = 7.3–99 mcg/ml)[25]. Neither concentration might be a good indicator of the *in vivo* target and choosing either as the "effective concentration" could lead to an order of magnitude error in target concentration.

*Thrombelastograph*

The thrombelastogram (TEG) measures functional defects in coagulation, from fibrin formation through platelet aggregation to fibrinolysis[26]. TEG data have been used successfully to predict neonatal sepsis[27], haemostatic changes in paediatric

neurosurgical patients[28] and for the management of coagulopathies after CPB in children[7]. This tool offers a potential effect measure of fibrinolysis in children undergoing CPB but its role is yet to be defined[7,29].

Quantification of TEG variables is shown in Figure 1. The reaction time (r) represents the rate of initial fibrin formation and is related functionally to the intrinsic coagulation pathway. The clot formation time (K) reflects the rapidity of fibrin build up and cross-linking as the clot forms. The α-angle reflects the speed at which solid clot forms. The maximum amplitude (MA) is a reflection of the absolute strength of the fibrin clot. This is influenced by fibrinogen concentration, platelet numbers, platelet function and factors VIII and XIII. The $A_{60}$ value (amplitude at 60 min) is useful in measuring clot retraction or destruction by comparing it to the MA value. An $A_{60}$/MA ratio (whole blood clot lysis index) less than 0.85 has been used to define fibrinolysis[15,26]. The time required to determine the $A_{60}$/MA ratio is longer than clinically desirable in some cases.

Measurement of the K phase and MA have proven useful for monitoring coagulation after cardiac surgery. Children (4.9 yr, range 0.1–16 yr, *n*=22) with a postoperative blood loss of more than 0.7 ml/kg/h have a prolonged K phase, showing impaired fibrinogenesis and a decreased maximum amplitude (MA), suggesting inadequate clot stability and platelet function[29]. The specificity of TEG prediction of future bleeding was 73%[29].

## Lysine analogues

Plasminogen has a lysine binding site by which it attaches to fibrin. Catalysed by tissue plasminogen activator, plasmin is formed from plasminogen. Blockade of the lysine binding site prevents plasmin induced fibrinolysis but not plasmin production. Other effects of plasmin may not be affected. Lysine analogues, such as tranexamic acid and epsilon aminocaproic acid (EACA) act by blocking the lysine binding site on plasminogen[30].

## Tranexamic acid (TA)

Tranexamic acid (trans-4-aminomethyl-cyclohexane-1-carboxylic acid), a synthetic lysine analogue, is a competitive inhibitor of plasmin and plasminogen[24,31,32]. Plasmin inactivated with tranexamic acid (TA) retains its ability to inhibit thrombin-induced platelet activation, suggesting that TA inhibits plasmin's fibrin catalytic activity but not its binding to platelets. Both clot lysis and platelet dysfunction may contribute to bleeding after CPB. TA blocks plasmin-induced partial platelet activation during CPB, preserving platelet function and promoting haemostasis after CPB[25].

*Pharmacodynamics*

Prophylactic administration of TA decreases blood loss and blood transfusion requirement in both adult and paediatric cardiac surgery patients[6,32,33]. Clinical effect may be more pronounced in children with cyanotic heart disease than those with acyanotic heart disease[34]. Although a target plasma TA concentration of 10 mcg/ml[24] is sufficient to suppress fibrinolytic activity and suppression of plasmin-induced platelet activation occurs at 16 mcg/ml *in vitro*[25], effective *in vivo* concentrations are unknown. A minimum therapeutic plasma concentration of 20 mcg/ml has been suggested for patients undergoing CPB[4].

*Pharmacokinetics*

There are no pharmacokinetic or pharmacodynamic studies of TA in children undergoing CPB. TA is distributed throughout all tissues[24] and the elimination half-time is 120 minutes in adult patients without CPB, with the majority of the drug being recovered from the urine[31]. Renal insufficiency

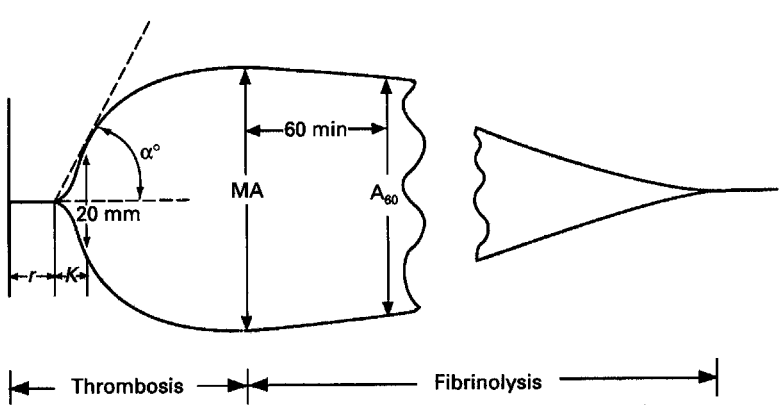


**Figure 1** A normal thromboelastograph (TEG) tracing.

reduces clearance[6]. TA pharmacokinetics have recently been described in adults undergoing CPB[4]. Data fit well to a two compartment model with adjustments for CPB. Parameter estimates were $V_1$ 10.3 l, $V_2$ 8.5 l, $Cl_{1O}$ 0.15 l/s and $Cl_{12}$ 0.18 l/s before CPB[4]. The elimination rate constant declined during bypass. The volume of distribution increased by 1.61 1 at the onset of bypass and remained at this level afterwards.

*Dosing*

A 30 minute loading dose of 12.5 mg/kg with a maintenance infusion of 6.5 mg/kg/h and 1 mg/kg added to the pump prime should maintain a TA concentration greater than 50 mcg/ml[4]. A higher dose based on 30 mg/kg loading dose plus 16 mg/kg/h continuous infusion and 2 mg/kg added to the pump prime would maintain TA concentrations greater than 125 mcg/ml[4]. These adult doses are higher than those associated with reduced blood loss during CPB (10 mg/kg over 20 min and 1 mg/kg/h infusion[6]) and reflect a lack of *in vivo* pharmacodynamic concentration-effect data.

Paediatric doses remain poorly described. A 50 mg/kg dose of TA given at induction reduced blood loss significantly in children (age 1 day-14 years) with cyanotic heart disease, but had no effect in those children with acyanotic heart lesion or those undergoing re-operations[34]. A subsequent study using higher doses showed an effect in acyanotic children[32]. Children presenting for repeat sternotomy and CPB (*n*=41, age 6 months-12 years) were given either TA (100 mg/kg, followed by 10 mg/kg/h) or saline placebo. At the onset of cardiopulmonary bypass, a second bolus of TA (100 mg/kg) or placebo was administered. Children who were treated with TA had 24% less total blood loss (26, SD 7 *vs* 34, SD 17 ml/kg) compared with children who received placebo[32].

Paediatric studies have addressed neither pharmacokinetic changes with age nor the dilution effect of the relatively large CPB circuit prime in the very young. TA is cleared renally and renal function matures over the first 6 months of life[35], dictating changing dose requirements with age to achieve a prescribed target concentration. CPB in children is usually performed with hypothermia, mainly to afford cerebral protection, while some procedures require deep hypothermic circulatory arrest (15 °C). The effect of hypothermia on TA clearance or disposition is unknown. Further, concentration-effect relationships remain undefined, partly because of the difficulty in defining a satisfactory effect measure.

*Toxicity*

Complications attributable to TA in adult patients after CPB are infrequent. The most pressing concern is that TA may promote a hypercoagulable state. Cases of cerebral, pulmonary, mesenteric and retinal thrombosis have been reported in adults[32], but reports in children are rare.

Thrombotic complications after CPB can be catastrophic and may occur without the use of antifibrinolytics. Risk benefit analysis of antifibrinolytic drug use is difficult in this situation. The expected benefit of decreased blood loss is only indirectly connected to improved outcome. The possibility of an increased incidence of relatively rare thrombotic complications will influence the decision to use the drug. Demonstrating an increased incidence of thrombosis may not be practical, given the large numbers of subjects required and the heterogeneity of the population. Restricting antifibrinolytic drug use to cases considered most likely to benefit (smaller children, cyanotic patients, patients having repeat operations) is one strategy employed to improve the risk benefit ratio.

## Epsilon Aminocaproic acid (EACA)

EACA is a synthetic antifibrinolytic agent. It is a lysine analogue that suppresses fibrinolytic activity by competitively inhibiting the binding of plasminogen and plasmin to fibrin. Prophylactic EACA administered intravenously (load, 150 mg/kg; infusion, 30 mg/kg/h) to 70 children at increased risk for bleeding (re-operation or Ross procedure) reduced intraoperative blood loss but did not significantly decrease blood product transfusions. The cause of this reduced effect is unknown but may be related to relative underdosing[36]. EACA is stated to be 10 times less potent than TA with a longer elimination half-life[30]. Comparison of the recommended EACA dosing with the higher doses recommended for TA suggests that the loading dose of EACA is inadequate (assuming a similar volume of distribution). The combination of the EACA (100 mg/kg) after induction, in the pump and for 3 hours after CPB plus aprotinin (10,000 KIU/kg) was slightly more effective than either drug alone in an infant study[37]. This combination, however, does not appear as beneficial as higher doses of aprotinin alone. Issues regarding thrombotic complications relating to EACA are the same as those described above for TA.

## Aprotinin

Aprotinin is a non-specific serine protease inhibitor. Serine proteases are involved in the coagulation, fibrinolytic and complement cascades

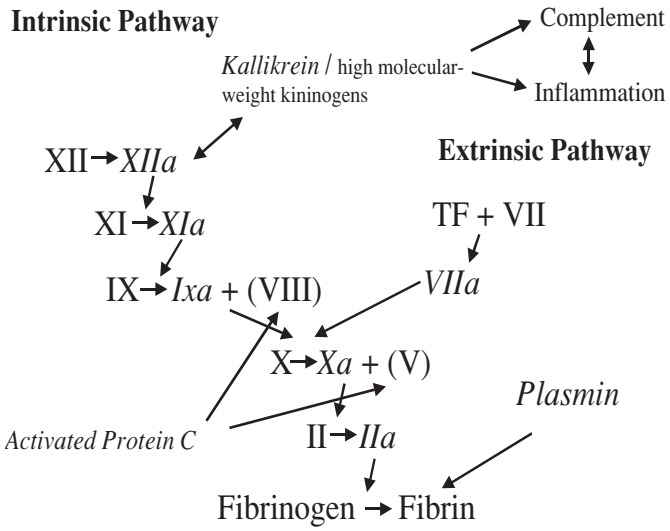


**Figure 2** Serine proteases in the coagulation cascade. Serine proteases are shown in italics

(Figure 2). Another target is the preservation of glycoprotein Ib receptors on the platelet membrane[38]. Aprotinin inhibits plasmin induced lysis of fibrin and may stabilise the platelet-fibrin haemostatic plug, reducing bleeding time. Lower doses of aprotinin are needed to inhibit plasmin than to inhibit kallikrein. There may also be some attenuation of the systemic inflammatory reaction (SIRS) induced by CPB[39], although this may be confined to lung parenchyma in children[3].

*Pharmacodynamics*

One study has shown that treatment with aprotinin decreased mortality almost two-fold in adults undergoing cardiac surgery (odds ratio 0.55, 95% CI 0.34–0.90) compared with placebo[40], but the benefit of this drug in low risk patients remains uncertain. Treatment with aprotinin and with lysine analogues decreased the frequency of surgical re-exploration (odds ratios 0.37, 95% CI 0.25–0.55 and 0.44, 95% CI 0.22–0.90 respectively). These two treatments also significantly decreased the proportion of patients receiving any allogeneic blood transfusion[40]. Aprotinin concentration is measured in kallikrein inhibitory units. One kallikrein inhibitory unit (KIU) is defined as the amount of aprotinin that decreases the activity of two biological kallikrein units by 50%[41]. Aprotinin (30,000 KIU/kg) effectively attenuated haemostatic activation and reduced blood loss and transfusion requirement in paediatric (<10 kg) cardiac surgery. Postoperative ventilation was also shortened when aprotinin was used[3]. The reported effectiveness of aprotinin varies and may be related to the dose given (15,000–60,000 KIU/kg), the paediatric age group studied and pathology (*e.g.* transposition of the great arteries vs. ventricular septal defect repair)[3,16,37,38,42,43]. Aprotinin's action on platelet function in the presence of cyanotic heart disease is unknown.

*In vitro*, plasmin is inhibited (50% effective dose) at a plasma aprotinin concentration of 125 KIU/ml, and kallikrein inhibition (50% effective dose) occurs at 200–250 KIU/ml[41]. It is postulated that a plasma concentration of 200 KIU/ml suppresses fibrinolysis and inhibits kallikrein in the clinical situation. This inhibition of kallikrein should attenuate the activation of coagulation, thus reducing thrombin generation and consumption of coagulation factors. Thrombin production normally has a positive feedback effect on the coagulation cascade[44]. The concentration of aprotinin for kallikrein inhibition based on *in vitro* studies (200–250 KIU/ml) may be insufficient during CPB, where there is high kallikrein activation and 90% inhibition of kallikrein requires concentrations closer to 500 KIU/ml[45]. There are no concentration-effect data available for children or adults. Kallikrein suppression is thought necessary for the suppression of the inflammatory response to CPB. Lower concentrations of aprotinin are needed to inhibit plasmin than to inhibit kallikrein because aprotinin-plasmin binding is approximately 30 times stronger than aprotinin-kallikrein binding[2]. There is no predictive or significant relationship between aprotinin concentration at peak or end of CPB or surgery and the postoperative chest tube drainage[46]. There may be a relationship between the total dose of aprotinin and decrease in transfusion of allogeneic blood products[47,48], but this relationship is yet to be described adequately.

Decreases in blood loss related to aprotinin may relate not only to antifibrinolysis but also to preservation of platelet function. Aprotinin reduces platelet activation by plasmin, preserves platelet glycoprotein Ib receptors and reduces cyclooxygenase activity. Platelet adhesion and first-phase aggregation are independent of

cyclooxygenase. Thromboxane $A_2$ production and second-phase aggregation and release are cyclooxygenase dependent. Aprotinin reduces thromboxane $A_2$ production and attenuates β–thromboglobin release from α granules but does not affect platelet adhesion or thrombocytopaenia. The cyclooxygenase pathway is activated during CPB and aprotinin dampens this cascade by inhibiting kallikrein[2].

*Pharmacokinetics*

Aprotinin is a small, basic polypeptide completely filtered in the glomerulus and metabolised by lysosomal enzymes in the proximal convoluted tubule[49,50]. Aprotinin is predominantly lost from the plasma by binding to the endothelium[46]. Aprotinin, like heparin, is also taken up by macrophages and is found in the mast cell[46]. Protein binding is low. Aprotonin has a volume of distribution at steady state (Vdss) of 20 l, a clearance of 35–53 ml/min and a *t*½ of 5.3–8.3 h in adult patients[51,52]. Clearance is reduced (25 ml/min) and *t*½ is prolonged (19.9 h) in patients with renal insufficiency or end stage renal disease undergoing CPB[51]. The pharmacokinetics of aprotinin in adult patients undergoing CPB are poorly defined and there are no data for children.

*Dosing*

Two studies suggest that lower plasma concentrations are achieved in children than in adults given similar doses on a per kilogram basis[3,16]. These results are supported clinically. An aprotinin dose of 50,000 KIU/kg had less effect in children, using euglobulin lysis time as an effect marker, than in adult patients[42].

Current dose regimens in children vary and do not account for changes in clearance or the coagulation cascade with age, pathology, CPB prime solution or hypothermic technique[53]. Extrapolation from adult dosing[16,54] has been made using either per kilogram or surface area models, neither of which may be appropriate for small children[55]. An initial dose of 30,000 KIU/kg at induction of anaesthesia and a further 30,000 KIU/kg in the CPB pump prime has been suggested[16]. This group of researchers has subsequently suggested 30,000 KIU/kg at induction and a fixed dose of 50,000 KIU in the pump prime in children <10 kg[3]. Higher doses of 50,000 KIU/kg at induction of anaesthesia, 50,000 KIU/kg in the pump prime and an intraoperative infusion of 20,000 KIU/h have also been suggested in children <15 kg, although additional benefit is unproven[38]. Others were unable to demonstrate improved effect with a dose of 240 mg/m$^2$ (~70,000 KIU/kg compared to 120 mg/m$^2$ (~35,000/kg) in children aged 0.5–11.3 years[56].

*Toxicity*

Anaphylactic reactions to aprotinin have been described. The severity of the reaction ranges from mild (no intervention) to severe (longer-lasting circulatory depression despite vasopressor therapy). Patients with an interval less than 6 months since the previous exposure have a higher incidence of adverse reactions than patients with a longer interval (4.5% *vs* 1.5%). If a patient requires re-exposure to aprotinin, then histamine $H_1/H_2$ receptor blockade and a small test dose prior to full dosing is suggested. The benefits of aprotinin treatment in complex congenital paediatric heart surgery are believed to outweigh the relative risk of a serious allergic reaction[57].

Concerns about rare catastrophic thrombotic complications of aprotinin, similar to those described for TA above, have also been raised. The practical dilemma in assessing this for aprotinin is similar, but the balance may differ. The potential benefits of aprotinin may be greater due to the anti-inflammatory actions, and the risks may be less due to the inhibition of excess activation of the coagulation pathway.

It is possible that patients with a predisposition to thrombosis may be at particular risk of thrombosis when antifibrinolytic drugs are administered. This has not been studied *in vivo*, but the action of aprotinin, in a CPB model, on blood from normal subjects and blood from subjects heterozygous for Factor V (Leiden) (FVL) mutation has been examined[58]. Activated protein C (APC) usually decreases Factor V activity, but subjects with the FVL mutation are less sensitive to this action. FVL is the commonest form of inherited thrombophilia. Aprotinin inhibits APC (a serine protease) which could further compound the thrombotic tendency of patients with the FVL mutation. The adverse effects of both CPB and aprotinin on the action of APC (measured by the APC ratio) were confirmed in the *in vitro* CPB model, with the lowest ratios found in subjects with FVL.

Analogous to the increasing examination of genetically based thrombophilia as risk factors in adult cardiac medicine, it is possible that these same tests may eventually have a use in paediatric cardiac surgery.

## Desmopressin

Desmopressin is a synthetic analogue of vasopressin. It increases concentrations of coagulation factor VIII C, von Willebrand factor (vWF) and tissue plasminogen activator, by liberating these from storage sites in reticuloendothelial cells.

Large multimers of vWF are also formed and act as "glue" linking platelets to subendothelial cells. Circulating vWF stabilises factor VIII C and increases blood coagulability. The use of desmopressin results in a small decrease in perioperative blood loss, but is not associated with a beneficial effect on other clinical outcomes [40]. The routine use of desmopressin is not recommended for cardiac surgery.

## Cost

The lysine analogues are substantially cheaper than aprotinin. In adult practice, this has influenced the choice of these agents ahead of aprotinin, which is relatively expensive to use in adults. The cost benefit ratio for the use of these agents in neonates is different to that in adults, and is more favourable to aprotinin. In neonates, the absolute dose of the drugs is so small that the cost of aprotinin becomes relatively small. As neonates have a greater inflammatory reaction to CPB and aprotinin may have wider benefits in suppressing that response, the potential benefits may be greater than in adults. An approach adopted by some CPB surgical teams is to restrict aprotonin to children undergoing repeat surgery or surgery involving deep hypothermic arrest and to use TA for less complex cases.

## Conclusions

The benefits of the antifibrinolytic drugs in neonates, infants and children are well described, but dose regimens are empirical. Regimens extrapolated from adult pharmacokinetic or dose data using surface area or weight may over- and under-estimate respectively[55] and have not considered pharmacokinetic maturation changes over the first year of life. Clearance of aprotinin and TA is renal and the kidney is immature in infancy. The influence of hypothermia, the systemic inflammatory response, CPB circuitry and relative prime volumes are missing from paediatric analyses. Paediatric cardiac operations are mostly for congenital disorders, unlike adult surgery that is for degenerative disease (*e.g.* coronary artery narrowing). Congenital heart disease may be associated with other organ dysfunction (*e.g.* renal or hepatic compromise), reduced growth, poor nutritional status and bleeding diathesis. Pharmacodynamics may also be altered in infancy because the coagulation cascade is immature. The effects of concomitant drug therapy that may also affect coagulation are unknown.

The lack of clinical effect measures that can be used to describe concentration-response data has led to the use of target concentrations determined from *in vitro* studies that may not be applicable *in vivo*. TEG may prove a useful clinical marker of antifibrinolytic effect. Potential benefits of antifibrinolytic therapy should consider outcomes beyond blood loss and may be influenced by effects not directly related to antifibrinolysis, especially for aprotinin. Assessment of changes in the risk of thrombosis relating to the use of antifibrinolytics, is crucial but data is not available. It is likely that this risk will differ with the different agents and between individuals. Restricting the use of antifibrinolytics to cases at risk of excessive bleeding (or likely to benefit from effects other than antifibrinolysis) is likely to improve the risk benefit ratio.

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Paper PPDT–0102, *Accepted for publication:* 17 February 2004
*Published Online:* 18 June 2004
doi:10.1185/146300904125004146