

# Aprotinin should not be used routinely in infants and children undergoing complex open heart surgery

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## Introduction

It is instructive that, despite multiple studies involving many thousands of patients, the indications for aprotinin in adult cardiac surgery remain controversial and are currently under FDA scrutiny.

[<http://www.fda.gov/CDER/DRUG/infopage/aprotinin/default.htm>] Aprotinin should not be administered routinely to infants and children undergoing complex open-heart surgery (OHS). This position will be supported by examination of the pediatric literature and presentation of selected aspects of the adult debate.

Aprotinin (Trasylol; Bayer Corporation, Pittsburgh, PA) is a nonspecific serine protease inhibitor derived from bovine lung. The drug was discovered in Munich in the 1930's as a kallikrein inhibitor. Initially released in 1959 for the treatment of pancreatitis, its application to cardiac surgery followed the observation by Royston and colleagues in 1987 that the agent had beneficial effects on hemostasis. Aprotinin inhibits coagulation contact activation and modifies the inflammatory response. It prevents platelet activation by inhibiting the action of thrombin on the protease-activated receptor 1 and binds to plasmin to inhibit fibrinolysis. After protein C is activated by thrombin in the presence of endothelial thrombomodulin, aprotinin inhibits the inactivation of factors V and VIII. The drug is metabolized and eliminated by the kidneys. Aprotinin is the only antifibrinolytic approved by the FDA "for prophylactic use to reduce peri-operative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass (CPB) in the course of coronary artery bypass graft surgery". No antifibrinolytic has received FDA approval for OHS in children. Reported benefits of aprotinin include reduction in perioperative bleeding and blood product transfusions, reduced inflammatory response to CPB and reduced incidence of postoperative stroke in selected adult patients. Risks include anaphylaxis, renal dysfunction and thrombosis. The drug is expensive but may be cost effective compared to placebo.

Routine administration of aprotinin to children undergoing complex OHS can only be accepted if the drug is consistently efficacious compared to placebo and superior to alternative therapies in efficacy and/or safety and/or cost. The heterogeneity of congenital heart disease makes it difficult to define which procedures are complex. Multiple factors are associated with increased bleeding, including young age, complex surgical repairs, degree of hypothermia, duration of CPB, cyanosis, pre-existing coagulopathy, reoperation, and use of mechanical support devices.[1] Some utilize aprotinin for all cases other than "closed" cases and simple two-ventricle OHS (ie, atrial septal defect repairs or ventricular septal defect repairs).[2] Others hardly ever use it.[3] Blood conservation is a worthy endeavor because excessive bleeding is associated with increased morbidity, blood transfusion can lead to significant complications and banked blood products are a diminishing resource.[4]

## **Is aprotinin an efficacious antifibrinolytic?**

Numerous randomized, placebo-controlled trials in adult patients have demonstrated that aprotinin reduces perioperative blood loss and red blood cell transfusions by about 30% [5, 6] but pediatric studies have been much less convincing.[7, 8] Davies and colleagues studied 42 patients designed to receive placebo or aprotinin and found aprotinin to be of no benefit in routine cardiac operations.[9] Boldt et al. found less than 35,000 KIU/kg aprotinin did not reduce postoperative blood loss.[10] In another study, no beneficial effect of aprotinin on blood loss could be demonstrated in patients with ventricular septal defect or tetralogy of Fallot, in terms of blood loss and transfusion requirements, but only in patients with complex cardiac pathology such as transposition of great arteries.[11] In contrast, it was shown that aprotinin reduced operative closure time and blood use in pediatric patients undergoing primary OHS who were 6 months of age or less or who underwent reoperation.[12] Efficacy for reduction in transfusion requirements has been demonstrated for reoperative surgery [13, 14] and patients with cyanotic heart disease.[15, 16] Univariate analysis of outcome following first stage palliation of hypoplastic left ventricle suggested aprotinin administration might be a useful survival strategy but multivariate analysis did not show it as significant.[17] Recently, a meta-analysis of 626 children from 12 randomized controlled trials of aprotinin was conducted.[18] Aprotinin reduced the proportion of children who received red blood cell or whole blood transfusions during cardiac surgery by 33% (relative risk = 0.67; 95% confidence interval, 0.51 to 0.89). Aprotinin did not have a significant effect on the volume of blood transfused or the amount of chest tube drainage. The authors commented that “most of the studies were of poor methodological quality”. “Among trials examining the effect of aprotinin in children, there is a need for consistency in reporting dosing regimens and transfusion requirements using objective transfusion protocols. Before the routine use of aprotinin in children undergoing cardiac surgery can be recommended, further independent randomized controlled trials (RCTs) are needed to carefully examine clinically important outcomes including bleeding, reoperation rates, and death in addition to the need for perioperative transfusion.”

Each study in the meta-analysis used a different dose regimen. Oliver demonstrated a strong positive relationship between weight and aprotinin concentration before and during CPB when weight-based dosing was used.[19] The antifibrinolytic activity of aprotinin occurs at a concentration as low as 50 KIU/mL but the anti-inflammatory activity associated with kallikrein inhibition requires a much higher plasma aprotinin concentration (>200 KIU/ml). Studies in neonates and infants have been at variance regarding transfusion requirements and blood loss and it may be that small patients do not attain aprotinin concentrations believed to confer anti-inflammatory or even antifibrinolytic activity with current aprotinin weight-based dosing regimens. Interestingly, similar observations in adult patients were reported recently.[20]

In summary, the data indicates the efficacious dose of aprotinin for children is unknown Also, demonstration of efficacy versus placebo is far less convincing than corresponding adult data and relies on evidence of problematic methodology. As stated by Oliver, “Because severe allergic reaction, thrombosis, and renal dysfunction may occur with aprotinin, its use may be unwarranted in certain high-risk infants and children until efficacy is better established”.[19]

### **Is aprotinin superior in efficacy to other antifibrinolytics?**

If aprotinin and the lysine analogues have equivalent efficacy, then aminocaproic acid or tranexamic acid might be the more appropriate choice because, apart from their lower cost, they are entirely synthetic and risks of disease transmission should be inexistent. Moreover, the likelihood of inducing an anaphylactic reaction after re-exposure are much lower than those reported for aprotinin.[21]

In a meta-analysis of adult data, 13 head-to-head studies comparing aprotinin with tranexamic acid were identified and their results pooled [22]. Overall, these trials showed a reduction in mean blood loss with aprotinin compared to tranexamic acid, which was statistically different, but with limited clinical significance (106 mL). Recently, this data was updated with additional studies and re-analysis found there was no difference in the blood-conserving properties between aprotinin and tranexamic acid.[23]

Only a few lysine analogue studies have been performed in children undergoing OHS. An early study reported a 42% reduction in bleeding in cyanotic patients receiving epsilon aminocaproic acid.[24] In a double-blind study, there was no significant difference in postoperative blood loss in acyanotic children undergoing OHS who received either a placebo dose or a single dose of tranexamic acid. However, when the children with cyanosis were analyzed separately, there was a highly significant difference in blood loss between the groups.[25] Isetta et al. reported that in children, tranexamic acid plasma concentration between the post-bolus peak and the end of CPB has an 80% decline when a continuous infusion was not used.[26] In some other studies, it is reported that a large dose of tranexamic acid effectively reduces blood loss in children undergoing cardiac reoperation.[27, 28] Chauhan and colleagues found both epsilon aminocaproic acid and low dose aprotinin to be equally efficacious compared to placebo in reducing postoperative blood loss and packed red blood cell and platelet requirements in children with congenital cyanotic heart disease.[16] In a later study, aminocaproic acid and tranexamic acid were equally effective in reducing postoperative blood loss, as well as blood and blood product requirements in children with cyanotic heart disease undergoing OHS as compared with the control group.[29]

In summary, while there is insufficient data to recommend the routine use of lysine analogues for complex pediatric OHS, published literature suggest the blood conservation properties of these agents are equivalent in efficacy to aprotinin.

### **What about aprotinin's anti-inflammatory properties?**

Some proponents argue that aprotinin has benefits beyond blood conservation, such as offering neurological protection owing to its action on protease-activated receptors.[30] There is, however, no clinical evidence that aprotinin reduces the risk of stroke in adults beyond those that can be explained by reduction of blood loss. This holds true for other reported benefits of aprotinin such as shorter time on the ventilator, shorter duration in intensive care, reduced inotrope requirements, lower pulmonary vascular resistance and cost.[13, 14, 31, 32] Thus, until the organ-protective effects of aprotinin are demonstrated in studies that compare aprotinin with other antifibrinolytic drugs, this argument has no merit.

### **What about other blood conservation and anti-inflammatory therapies?**

Antifibrinolytics are only one component of the overall blood conservation and anti-inflammatory strategy.[3] Standardization of measures such as steroid administration, ultrafiltration, red cell salvage, transfusion triggers, transfusion algorithms and conduct of CPB are important when comparing different studies. Better alternatives to antifibrinolytic therapy exist in some cases. For example, avoid CPB! At our institution, CPB is not required for the majority of bidirectional Glenn and Fontan procedures.

### **What is the relative safety of antifibrinolytic drugs?**

This is an important question if the available antifibrinolytic agents are of equivalent efficacy. All the pediatric studies, including the meta-analysis of aprotinin, are clearly underpowered to address issues of safety. Therefore, consideration of adult data is necessary. Recent publications have embroiled this topic in controversy and uncertainty.[33, 34] To properly assess the relative safety profile of antifibrinolytic drugs, it is important to consider both the results of systematic reviews of placebo-controlled RCTs and the results of large observational studies. Methodologically pristine RCTs may not necessarily be the best means for identifying drug toxicity. This is particularly true if the associated harms are rare, delayed, or unrelated to the therapeutic indication of the drug. Large observational studies, with appropriate multivariable risk-adjusted analysis to control for the known confounding factors, may be better suited for detecting such drug side effects.[35] These large databases have the advantage of representing both the true clinical scenario and the entire population.

When considering the placebo-controlled RCTs, it is important to remember that many adverse events such as stroke, renal failure, myocardial infarction, and death are directly related to excessive bleeding. Because antifibrinolytic drugs decrease excessive bleeding, they should be associated with reduced adverse event rates in placebo-controlled studies. Reassuringly, systematic reviews of these studies found that, when compared with placebo, the point estimates for adverse event rates were, for the most part, decreased by both classes of drugs.[6, 36] Notably, the meta-analysis of the placebo-controlled trials found no reduction in renal failure or myocardial infarction, despite a 30% reduction in transfusion, when aprotinin was used as an antifibrinolytic.[23]

Mangano et al. [37] performed a retrospective analysis of 4374 patients and found aprotinin use was associated with an increased risk of renal dysfunction (controls, 2% vs aprotinin group, 5%,  $p=0.001$ ) and renal failure (controls, 1% vs aprotinin group, 5%,  $p=0.01$ ) for patients undergoing primary CABG or complex CABG surgery. They also noted a 55% increase in the risk for myocardial infarction or heart failure and a 181% increase in risk for stroke or encephalopathy for patients undergoing primary CABG surgery who received aprotinin when compared with control patients. Karkouti et al. [34] performed a propensity score case control comparison of 898 high-transfusion risk patients undergoing cardiac surgery who received either aprotinin or tranexamic acid. A greater percentage of patients receiving aprotinin developed renal dysfunction in the first postoperative week when compared with those receiving tranexamic acid (24% vs 17%,  $P=0.01$ ). These findings have provoked extensive debate.[38, 23, 39, 36, 37, 40, 41, 42, 43, 44, 45]

There are numerous case reports of thrombosis-related morbidity and mortality following the use of antifibrinolytic agents. It is unclear whether the risk of thrombosis

differs between drugs. Early reports of increased graft and other thromboses after aprotinin administration may have been due to inadequate heparinization in the presence of aprotinin.[47] Of note, to achieve the same activated clotting time, children under one year of age require higher heparin doses per kilogram of body weight than older patients.[21]

The risk of anaphylaxis is considerably higher for aprotinin than for the other antifibrinolytic agents. On re-exposure to aprotinin, the risk of anaphylaxis was estimated to be about 2.8%, with a fatality rate of 9% and 72% of reactions occurring within 3 months of the previous exposure. Anaphylaxis on first known exposure was uncommon.[48] It is important to appreciate that many topical fibrin sealants contain aprotinin and can sensitize the patient to aprotinin. Jacquiss and colleagues reviewed 865 exposures to aprotinin in children of which 184 were re-exposures.[2] Reactions occurred in 7 of 681 (1.0%) first exposures and 3 of 184 (1.6%) repeat exposures. The reactions were described as severe (cardiopulmonary instability) in 80% of cases. In contrast to other (mainly adult) studies, the incidence or reactions on first exposure was higher and reactions on re-exposure were not more likely with a shorter time interval between exposures. Skin testing and IgE assays were not helpful.

The majority of children with complex heart disease (e.g.: single ventricle physiology) will require repeat surgery. If one considers the drugs anesthesiologists typically administer during cardiac anesthesia, only protamine can rival aprotinin's risk of allergic reactions. Unlike protamine, there are good alternatives to aprotinin.

### **Commercial considerations**

Apart from the high cost of aprotinin, there are several other issues worthy of note. Firstly, industry-sponsored trials have been associated with inflated estimates of benefit [49] and some such studies were included in the pediatric and adult meta-analyses of aprotinin. Secondly, on September 21, 2006, FDA held a public meeting of the Cardiovascular and Renal Drugs Advisory Committee to discuss the safety and overall risk-benefit profile for Trasyolol. At that meeting, the committee discussed the findings from the two published observational studies, the Bayer worldwide safety review, and the FDA review of its own post-marketing database. On September 27, 2006, Bayer Pharmaceuticals told FDA that it had conducted an additional safety study of Trasyolol.

The preliminary findings from this new observational study of patients from a hospital database reported that use of Trasyolol may increase the chance for death, serious kidney damage, congestive heart failure and strokes. FDA was not aware of these new data when it held the September 21, 2006, Advisory Committee meeting on Trasyolol safety. This lack of transparency by Bayer was harshly criticized in the lay (New York Times editorial Oct 4, 2006) and medical press.[37, 50, 51] Discerning physicians should probably bear these matters in mind when reviewing aprotinin literature.

### **FDA recommendations**

At the time of going to press, FDA recommendations remain as follows:

- Physicians who use Trasyolol should carefully monitor patients for the occurrence of toxicity, particularly to the kidneys, heart, or brain, and promptly report observed adverse event information to Bayer Pharmaceuticals, the drug manufacturer, or to the FDA MedWatch program.

- Physicians should consider limiting Trasylol use to those situations where the clinical benefit of reduced blood loss is essential to medical management of the patient and outweighs the potential risks.

It is plainly apparent that routine administration of aprotinin falls outside these recommendations.

### **The future**

Important questions remain about the use of antifibrinolytic drugs. Which of the drugs is most effective in high-risk cases? Do any of the antifibrinolytic drugs offer benefits beyond limiting blood loss? Do other drugs (for example, activated Factor VII) offer a better efficacy and safety profile? Well-designed, head-to-head, clinical trials are required. An ongoing Canadian trial (BART) in adults may provide some insights.[52]. Presently, the routine use of aprotinin in patients undergoing cardiac surgery with CPB cannot be recommended outside of the experimental setting and the antifibrinolytic of choice today is a lysine analogue.

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