

Safety of Aprotinin Use and Re-Use in Pediatric Cardiothoracic Surgery

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Background—Hypersensitivity reactions to aprotinin have been reported in adult cardiac surgical patients undergoing initial and re-exposure to the medication. This study describes the incidence and impact of aprotinin hypersensitivity reactions in children undergoing cardiothoracic surgery.

Methods and Results—In this retrospective review of our entire experience with aprotinin (n=865), 681 first exposures, 150 second exposures, and 34 third or higher exposures were examined. Reactions were classified as mild (generalized cutaneous erythema, Type A) or severe (unexplained cardiopulmonary instability after aprotinin exposure, Type B). Records of patients sustaining a reaction were reviewed to assess the impact of the reaction on outcome and to survey reaction management strategies. Reactions occurred in 7 of 681 first exposures (1.0%), of which 2 were Type A and 5 were Type B. In second exposures, there were reactions in 2 of 150 (1.3%), of which both were Type B. In 34 third or higher exposures, there was only 1 reaction (2.9%), which was Type B. Reactions were no more likely on second, third, or higher exposure than on initial exposure. Skin testing had a negative predictive value of 98.9% and a positive predictive value of 20%. Anti-aprotinin IgE was undetectable in 7 of 8 reactor cases tested. No adverse sequelae were attributed to aprotinin reaction.

Conclusions—The risk of hypersensitivity reactions to aprotinin is low in children undergoing cardiothoracic surgery, even with multiple exposures to the medication. Reactions are more likely with re-exposure, and risk increases with multiple exposures. Neither skin testing nor assays for IgE identified reactors. (*Circulation*. 2002;106[suppl I]:I-90-I-94.)

Key Words: heart surgery ■ heart defects, congenital ■ drug administration ■ extracorporeal circulation

Aproinin is a serine protease inhibitor that was first used as an antiinflammatory agent in the treatment of acute pancreatitis in the 1960s. Because of its antifibrinolytic effect, it was subsequently used therapeutically to treat patients with excessive postoperative bleeding after open heart surgery.¹ By late 1980s, prophylactic aprotinin had been shown to be efficacious in reducing blood loss and transfusion in adults undergoing cardiac surgical procedures.^{2,3} The application of aprotinin to pediatric cardiovascular procedures with their inherently high risk of bleeding naturally followed.^{4,5} Additional interest in the use of aprotinin in pediatric cardiac surgery resulted from the demonstration in aprotinin-treated patients of improved oxygenation and reduced pulmonary gradients in children with univentricular hearts undergoing cavopulmonary anastomosis and the Fontan procedure.⁶ Another potentially salutary effect of aprotinin is the reduction of bypass-induced inflammation as demonstrated reduced levels of pro-inflammatory cytokines in aprotinin-treated patients,⁷⁻⁹ although the clinical significance of these reductions remains to be shown. A neuroprotective effect of aprotinin in patients undergoing cardiopulmonary bypass has recently been suggested.¹⁰

Despite the many real and potential benefits of the use of aprotinin, there has been significant concern about hypersensitivity-type reactions especially on reexposure, because aprotinin is a foreign polypeptide extracted from bovine lung. Antibody formation has been demonstrated in 25% to 50% of adult patients receiving the drug.¹¹⁻¹³ There are numerous reports of severe reactions to aprotinin, both on primary and secondary exposure, with the majority described in adult patients.¹³⁻²⁰ The present study was undertaken to review our experience with aprotinin reactions in a population undergoing congenital cardiothoracic surgical procedures.

Methods

Subjects

The subjects of this report are all patients who received aprotinin at the Children's Hospital of Wisconsin from our first usage in March 1994 through September 2001. Included are a total of 865 exposures in 681 patients. There were 150 second exposures and 34 third or higher exposures. The patients ranged in age from newborn to 42.6 years of age (median 1.0 years).

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TABLE 1. Details of Hypersensitivity Reaction/Positive Skin Testing on First Aprotinin Exposure

Patient No.	Diagnosis	Operation	Description of Reaction Type	Reaction Treatment	Received Full Aprotinin Dose
1	DORV, prior PAB	Repair DORV, takedown PAB	generalized erythema-A	diphenhydramine	Yes (decreased loading rate)
2	Recurrent sub-PS	Resect sub PS	generalized erythema-A	none	Yes
3*	HLHS	Cavopulmonary shunt	+ve skin test—	none	Yes
4	Multiple VSD, prior PAB	Repair VSD, takedown PAB	hypotension flushing-B	epinephrine, diphenhydramine	No
5	Sub AS	Resect sub AS	hypotension—B	none	No
6	Muscular VSD	VSD repair	hypotension, ST depression—B	epinephrine	Yes
7	LVOT obstruction, primum ASD	Resect subaortic obstruction	hypotension, tachycardia—B	diphenhydramine, solumedrol, saline bolus	No
8	TAPVR, TGA	Repair TAPVR	hypotension—B	saline bolus	Yes

DORV indicates double outlet right ventricle; PAB, pulmonary artery band; sub PS, sub-pulmonic valve stenosis; HLHS, hypoplastic left heart syndrome; VSD, ventricular septal defect; sub AS, aortic valve stenosis; LVOT, left ventricular outflow tract; TAPVR, total anomalous pulmonary venous return; TGA, transposition of great arteries.

*Patient 3 had an initial Norwood operation at another institution and a review of the hospital records could not eliminate the possibility of aprotinin exposure so skin testing was performed.

The pattern of usage changed over the years of the study. Initially, the drug was used only in selected patients who were felt to be at particularly high risk for bleeding. Encouraged both by our initial anecdotal experience with its blood-conserving effects and by reports of broader efficacy in reducing cardiopulmonary bypass-associated inflammation, we have significantly liberalized usage of the drug. Presently, we employ aprotinin in all neonatal operations requiring cardiopulmonary bypass, all operations requiring cardiopulmonary bypass for single ventricle anatomy, all reoperations, cardiac and pulmonary transplantation, and in any circumstance in which there is any increased risk of bleeding. The only operations in which aprotinin is not used are “closed” cases and simple two-ventricle “open” cases (ie, atrial septal defect repairs or ventricular septal defect repairs).

Intraoperative Management

Aprotinin was administered according to the following high-dose protocol, which did not change throughout the study period: 1.7×10^6 kallikrein inactivator units (KIU)/m² as an intravenous loading dose, 1.7×10^6 KIU/m² in the extracorporeal circuit prime, and a continuous infusion during the operation at 4.0×10^5 KIU/m²/hr. For patients with a known or suspected prior aprotinin exposure, skin testing was accomplished with both a skin puncture test using undiluted drug (DermaPIK Greer Laboratories, Lenoir, NC) and an intradermal injection (0.1 cc of 1:100 dilution). The puncture test employed a positive (histamine) and a negative (saline) control. The intradermal test employed a negative control (saline). The “wheal and flare” reaction was interpreted after 15 minutes. In all patients an intravenous test dose of 1.0×10^5 KIU was administered 10 minutes before the full loading dose. The timing of the administration of aprotinin administration was usually arranged to provide the loading dose just before the initiation of cardiopulmonary bypass. The bypass prime dose was delayed until the patient had demonstrated tolerance of the intravenous and skin test doses.

Patients did not receive prophylactic corticosteroids or antihistamines in anticipation of aprotinin administration. As part of another protocol, in the past 24 months neonates undergoing surgery requiring cardiopulmonary bypass received intravenous corticosteroids, typically 6 hours preoperatively, which would not be expected to prevent an immediate hypersensitivity reaction.

In the event of a suspected reaction to aprotinin, treatment was at the discretion of the attending anesthesiologist. No prospective protocol-driven reaction management strategy was employed. The decision to continue, modify, or terminate the administration of aprotinin was similarly made on an individual basis.

Data Collection and Analysis

A prospective database consisting of all patients receiving aprotinin has been maintained at Children’s Hospital of Wisconsin (CHW)

since the beginning of its use, and documents any adverse reactions potentially attributable to aprotinin. In the present study, after approval by the Institutional Review Board of CHW, hospital and clinic records were reviewed from all patients noted in the database to have a suspected reaction. The underlying diagnosis, type of surgery, date of surgery, interval since prior aprotinin exposure, management of the suspected reaction, and subsequent hospital course were recorded. Also noted was whether the full dose of aprotinin was administered. In some, but not all, patients suspected of having a reaction to aprotinin, blood was drawn in the operating room and an enzyme-linked immunosorbent assay (ELISA) for serum anti-aprotinin IgE was performed according to standard protocols. Patient samples were compared with samples from healthy controls and to a sample from a positive control patient with elevated specific IgE to aprotinin and a history of anaphylaxis with aprotinin administration.

Details of the suspected aprotinin reactions were analyzed and allowed the identification of 2 general classes of reaction. Mild reactions (Type A) were those in which the reaction was limited to generalized cutaneous erythema. Severe reactions (Type B) were those in which unexplained bronchospasm, generalized edema, hypotension, tachycardia, or ECG changes were noted in temporal relationship to the administration of aprotinin. Positive skin tests, defined as immediate formation of a wheal at the site of the skin puncture or intradermal injection, were also tabulated. Reaction rates were calculated for initial, second, and third or higher aprotinin exposures, and these rates were compared by Mantel-Haenszel Chi-square testing.

Results

First-Time Exposures

There were 681 patients who received aprotinin for the first time. In this group, there were 7 patients who experienced a reaction to the medication, of which 5 were Type B and 2 were Type A. The full dose of aprotinin was administered in 4 of the 7 patients who experienced a reaction. Diagnoses, operations, and details of reactions are shown in Table 1 for children sustaining reactions and positive skin tests on their first aprotinin exposure.

Reexposures

There were 150 patients who had a second exposure to aprotinin. In this group, there were 2 patients with adverse reactions, all of which were type B. Three patients had a

TABLE 2. Details of Hypersensitivity Reaction/Positive Skin Testing on Re-exposure to Aprotinin

Patient No.	Diagnosis	Operation	Time Since Last Aprotinin (days)	Description of Reaction—Type	Reaction Treatment	Full Aprotinin Dose
Second Aprotinin Exposure						
9	HLHS	Cavo-pulmonary shunt	119	+ve skin test	none	Yes
10	RVOT homograft stenosis	Homograft replacement	178	+ve skin test	none	Yes
11	HLHS	Cavo-pulmonary shunt	238	+ve skin test	none	No
12	Repaired TOF	Close residual VSD	86	severe bronchospasm, +ve skin test—B	epinephrine, diphenhydramine	No
13	HLHS	Extracardiac Fontan	777	hypotension, ST depression, hypoxia—B	epinephrine	No
Third or Higher Aprotinin Exposure						
14	Heterotaxy	MBT shunt and AV valve repair	250	+ve skin test	none	Yes
15	HLHS	Decortication	171	hypotension, generalized erythema—B	epinephrine	No

HLHS indicates hypoplastic left heart syndrome; RVOT, right ventricular outflow tract; TOF, tetralogy of Fallot; VSD, ventricular septal defect; MBT, modified Blalock-Taussig; AV, atrioventricular.

positive skin test. In 2 of the 5 patients sustaining a reaction or positive skin test, the full dose of aprotinin had been administered. There were 34 patients who received a third or higher exposure to aprotinin. In this group, 1 patient had a type B reaction and 1 patient had a positive skin test. The patient with the positive skin test received the full dose of aprotinin, whereas the aprotinin administration was terminated in the patient with the severe reaction. The interval since last aprotinin dose was not different between those patients who had a reaction (median 178 days) and those patients who did not (median 214 days). Diagnoses, operations, interval since last aprotinin exposure, and details of reactions are shown in Table 2 for children sustaining reactions or positive skin test on reexposure.

Reaction Incidence and Consequence

The incidence of reaction to aprotinin was low in all groups (Table 3). Furthermore, there was no statistically significant difference in the reaction rates between first, second, or third or higher exposure. Even when all reexposures were grouped together, the rate of reaction was not different than the rate for initial exposure. The only demonstrable consequence of having either a type A or a type B reaction was that the patient was less likely to receive a full dose of aprotinin than if there had been no reaction. Specifically, there were no instances of postoperative hemodynamic, respiratory, renal, or neurologic

complication attributed to an aprotinin reaction in any of the 10 cases. In the entire cohort of patients receiving aprotinin no excess rate of thrombotic episodes was noted.

Skin Testing

There were 185 children who underwent skin testing before exposure to intravenous aprotinin (all second exposures, all third or higher exposures, and 1 patient receiving a first exposure but who had previously had cardiac surgery elsewhere). Of the 6 children with positive skin tests, 4 received the full dose of intravenous aprotinin without incident (false-positive skin tests), 1 went on to have a Type B reaction without receiving any additional aprotinin (true positive skin test), and 1 did not receive additional aprotinin and had no further reaction (unable to evaluate true versus false-positive). Thus the positive predictive value for aprotinin skin testing is only 20% (1/5). Of the 179 children with negative skin tests, 2 had Type B reactions on administration of intravenous aprotinin (false-negatives). Thus the negative predictive value for skin testing is 98.9% (177/179).

Serum IgE Assays

Of the 15 aprotinin reactions or positive skin tests, blood was drawn during the surgery and sent for an ELISA for anti-aprotinin IgE in 8 cases. In only 1 of these 8 children (which was a type B reaction in a child receiving aprotinin for the

TABLE 3. Incidence of Reactions to Aprotinin

	n	Total Reactions (%)	Type A—Mild Reactions (%)	Type B—Severe Reactions (%)	Did Not Receive Full Aprotinin Dose
First exposure	681	7 (1.0)	2 (0.3)	5 (0.7)	3
All re-exposures	184	3 (1.6)	0	3 (1.6)	3
Second exposure	150	2 (1.3)	0	2 (1.3)	2
Third or higher exposure	34	1 (2.9)	0	1 (2.9)	1

P=nonsignificant for comparison of rates of reaction for first vs second vs third or higher exposures.

P=nonsignificant for comparison of rates of reaction for first vs all re-exposures.

third time) was there detectable IgE. In the other 7 patients in whom the assay was performed, including 3 positive skin tests and 4 type B reactions, there was no detectable anti-aprotinin IgE. Assays for other immunoglobulin classes were not performed.

Discussion

This study confirms the safety of aprotinin use in pediatric patients undergoing primary and reoperative cardiothoracic surgery. The incidence of adverse reactions on reexposure to aprotinin (3/184 or 1.6%) is similar to that described in other predominantly adult series.^{12,19,20} The present report also documents a small but significant incidence of reaction in patients without documented prior aprotinin exposure. Although there are case reports of severe, anaphylactic reactions on initial aprotinin administration,^{13,14} the present study includes the largest collection of such events.

In contrast to other investigators,¹⁹ we did not observe reactions on reexposure to be any more likely with a shorter time interval between exposures. In fact, 2 of the 3 reactions observed on reexposure occurred at or beyond the 6-month interval suggested by Dietrich et al¹⁹ as the high-risk time for reexposure. Given the low absolute rate of reaction on reexposure, it is possible that the size of the present study is simply too small to demonstrate a time-related risk of reexposure. Alternatively, the risk may not actually be higher with earlier reexposure. In any case, we do not hesitate to reuse aprotinin early after initial exposure. For example, our practice in the surgical palliation of the hypoplastic left heart syndrome has been to perform the second stage operation (cavopulmonary shunt) between 3 and 6 months of age, always with aprotinin, and without any untoward consequences to date.

It is noteworthy that in this series approximately one half of the patients sustaining a reaction or positive skin test were nonetheless able to receive the full intended dose. The majority of these patients had only cutaneous reactivity, although 2 patients with severe reactions were able to receive the full dose. In those children with positive skin tests, the timing of the intravenous test dose and loading dose were delayed until just before the initiation of cardiopulmonary bypass, in case a reaction requiring bypass for resuscitation might occur.

Based on the experience described in this study, the value of routine percutaneous and intradermal skin testing may be questioned. Certainly, the very high negative predictive value (98.9%) allows a certain degree of confidence if the skin testing is negative. However, the dismal positive predictive value (20%) would needlessly prevent 80% of children with positive skin tests from receiving the drug. This disappointing experience with skin testing has been described by other investigators.^{11,12} We continue to perform skin testing, and in the event of a positive skin test the risk-benefit ratio of aprotinin use is reconsidered on an individual basis. Conversely, in the case of a negative skin test, the administration of aprotinin is still performed cautiously, bearing in mind that reactions to intravenous aprotinin occur despite negative skin testing. In either case, the administration of intravenous

aprotinin is generally delayed until just before the initiation of bypass.

In the group of 8 children who sustained reactions or positive skin testing on their first documented exposure to aprotinin, 6 were undergoing reoperations (see Table 1). In this group, details of the previous operations were incomplete with regard to the possible use of topical hemostatic agents, which may have contained aprotinin. Two were "closed" procedures and unlikely to have involved the use of topical agents, but 4 were "open" procedures during which topical hemostatic agents may well have been used. The importance of this detail, which could not be gleaned from the available records, is that topical preparations that contain aprotinin have been shown to induce anti-aprotinin antibody formation²¹ and even anaphylaxis on primary exposure.¹⁵ The potential for occult prior exposure and sensitization must therefore be borne in mind in children with previous surgical procedures in which aprotinin-containing sealants (for example Tisseel; Baxter Healthcare, Glendale, CA) may have been used. In such cases, despite the poor positive predictive value described previously, it would be reasonable to perform skin testing before intravenous aprotinin administration.

Because of the presumed allergic nature of aprotinin reactions, it might be expected that children demonstrating adverse responses to the drug would have detectable titers of anti-aprotinin antibodies. However, in this study, ELISA assays for IgE were negative in 7 of 8 children tested. This IgE positivity rate is lower than that previously reported in a survey of the literature by Scheule et al,²¹ in which 17 of 27 patients who had anaphylactic reactions to aprotinin had detectable levels of aprotinin specific IgE after reaction. We did not investigate levels of other antibody classes, including IgG4 which has been reported to cause "anaphylactoid" reactions on reexposure to an antigen.²² However, a recent study identified relatively meager positive predictive values for IgG and IgE assays (60% and 40%, respectively) in predicting reactions on reexposure.¹³ It is likely that antigen specific serum IgG is most useful in confirming prior exposure but of less utility in predicting which patients will exhibit a hypersensitivity reaction on reexposure.

In conclusion, our results demonstrate the safety of aprotinin use and reuse in cardiovascular surgical procedures in a pediatric population. The incidence of reactions to aprotinin is low in both primary and subsequent exposures. When reactions occur, they can be managed successfully, even to the extent of allowing continued administration of the drug in many cases. Furthermore, we have not identified any long-term ill effects of aprotinin reaction. Unfortunately, the ability to prospectively identify patients who will experience an adverse reaction on re-exposure is imperfect, with skin testing proving most useful in identifying those patients who will *not* have a reaction. Furthermore our limited experience with ELISA testing for anti-aprotinin IgE suggests that this *in vitro* test would not be clinically useful.

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