Hypersensitivity reactions to aprotinin re-exposure in paediatric surgery

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Abstract

Objective: Hypersensitivity to aprotinin is low (1–3%) but more likely with re-exposure. The manufacturer issued a black box warning which lists aprotinin re-exposure within 1 year of prior exposure as a contraindication. We investigated the temporal relationship between re-exposure interval and hypersensitivity in children. Methods: With Human Research Review Board approval, charts of all patients exposed to aprotinin during cardiac surgery were reviewed. We extracted data for re-exposure interval and hypersensitivity to skin tests, intravenous test dosing or infusion of the loading dose. We defined systemic hypersensitivity as haemodynamic instability, respiratory symptoms or diffuse skin reaction temporally related to exposure. Results: From March 1994 to June 2007, there were a total of 2333 aprotinin exposures in 1824 patients. A total of 509 re-exposures occurred in 381 patients: 280 in 244 patients with early (within 1 year) re-exposure and 229 in 222 patients with late (after 1 year) re-exposure. Thirteen systemic hypersensitivity reactions occurred in the 509 re-exposures (2.6%): two during skin testing and 11 during the loading dose. Although the incidence of local hypersensitivity was increased with early re-exposure (6/280 or 2.1% vs 0/229, p = 0.019), the incidence of the systemic reaction was not different between early and late re-exposures (6/280 or 2.1% (CI 0.8—4.6%) vs 7/229 or 3.1% (CI 1.2—6.2%), p = 0.6). Six patients with a previous hypersensitivity reaction had an additional re-exposure to aprotinin; one of these patients had a systemic reaction during the third exposure. Conclusion: The incidence and type of hypersensitivity to aprotinin re-exposure in our cohort is consistent with previous reports. Repeat exposure within 1 year did not increase the risk of systemic hypersensitivity.

Keywords: Aprotinin; Hypersensitivity; Anaphylaxis; Paediatrics

1. Introduction

Aprotinin is a serine protease inhibitor that has strong anti-inflammatory and anti-fibrinolytic activities because it inhibits kallikrein and plasmin and preserves platelet function [1—3]. Until recently, aprotinin was used prophylactically to reduce the risk of bleeding and to minimise cardiopulmonary-bypass-induced inflammation in cardiac-surgery patients at high risk for perioperative bleeding. The use of aprotinin appeared particularly appealing in children, because of a greater relative extracorporeal blood volume during cardiopulmonary bypass and, thus, increased blood component activation resulting in both inflammation and altered haemostasis.

Because it is a non-human protein extracted from bovine lung tissue, aprotinin carries a risk of sensitisation and hypersensitivity reactions. Antibodies to aprotinin have been detected in the serum after primary exposure in up to 50% of adults receiving the drug [4—6]. However, the reported incidence of clinically significant hypersensitivity to aprotinin in patients undergoing cardiac surgery is only 1—3% and occurs usually with re-exposure [7—9]. In a case series of adults and children by Dietrich et al., a re-exposure interval less than 6 months carried an increased risk of hypersensitivity with intravenous administration compared with longer intervals between exposures [7]. The reported risk of hypersensitivity led to a Food and Drug Administration (FDA) black box warning in December 2006 regarding the use of aprotinin: "The risk for anaphylactic or anaphylactoid reactions is increased among patients with prior aprotinin exposure and a history of any prior aprotinin exposure must
be sought prior to administration. The risk for a fatal reaction appears to be greater upon re-exposure within 12 months of the most recent prior aprotinin exposure.\textsuperscript{7} Re-exposure within a year of prior exposure was listed as a contraindication to use. However, in a smaller series from our institution by Jaquiss et al., a temporal relationship between re-exposure interval and the incidence of hypersensitivity was not apparent \textsuperscript{8}. Since that publication, the number of patients re-exposed to aprotinin at our institution has more than tripled. This follow-up study expands on our previous experience with aprotinin and compares the incidence of systemic hypersensitivity reactions upon early (within 1 year) re-exposure versus late (after 1 year) re-exposure.

2. Materials and methods

After Human Research Review Board approval, a retrospective, observational chart review of all surgical patients exposed to aprotinin was performed through the Children’s Hospital of Wisconsin patient database. A prospective database has been kept to document all exposures to aprotinin since it was first used for paediatric patients requiring cardiopulmonary bypass in March 1994. The comprehensive database included adults with congenital heart disease. All patients exposed to aprotinin on at least two separate occasions were included in this study. The age of the patient, diagnosis, operation, interval from previous aprotinin exposure, evidence of positive skin test, diffuse skin reaction or other systemic hypersensitivity reaction, management of reaction, hospital course and subsequent exposures, were recorded. Additional data for those patients with reactions include details pertaining to subsequent dose administration of aprotinin: none, partial or full.

As previously described by Jaquiss et al., aprotinin use at the Children’s Hospital of Wisconsin evolved from selective use in patients felt to be at highest risk for bleeding to routine use in the following populations when requiring cardiopulmonary bypass: neonates, patients with single ventricle lesions undergoing staged palliation, re-operations, cardiac and lung transplantation and any other patient deemed at high risk for bleeding \textsuperscript{8}.

Aprotinin was administered according to the following high-dose protocol: $1.7 \times 10^6$ kallikrein inactivator units (KIU)/\textsuperscript{m2} as an intravenous loading dose, $1.7 \times 10^6$ KIU/\textsuperscript{m2} in the extracorporeal circuit prime and a continuous infusion during the operation at $4.0 \times 10^5$ KIU/\textsuperscript{m2} h^{-1}. Aprotinin skin testing consisted of a skin puncture test and an intradermal injection (0.1 cc of 1:100 dilution). The skin response was observed for 15 min before consideration of intravenous administration. All patients received an intravenous test dose of $1.0 \times 10^5$ KIU 10 min before the full-loading dose. The intravenous aprotinin-loading dose was administered before the initiation of cardiopulmonary bypass with the cardiopulmonary bypass loading dose added to the circuit prime only if the patient developed no major hypersensitivity reaction during the intravenous test or loading doses.

Local hypersensitivity was defined as a local reaction to the subcutaneous or intradermal skin test. Systemic hypersensitivity was defined as haemodynamic instability, respiratory symptoms or generalised skin reaction alone or in combination when temporally related to aprotinin exposure during skin test, intravenous test dose, load dose or maintenance infusion. In the event of a local or suspected systemic reaction to aprotinin, symptomatic treatment was at the discretion of the attending anaesthesiologist, ranging from watchful waiting, interruption of the infusion to administration of epinephrine and intratracheal albuterol. A local reaction to the skin test was not considered an absolute contraindication to intravenous infusion because of its unknown predictive value. The decision to continue, modify or terminate the administration of aprotinin was made on an individual basis by the attending anaesthesiologist and cardiovascular surgeon. In some of the patients suspected of having a reaction to aprotinin, blood was drawn perioperatively to perform an enzyme-linked immunosorbent assay (ELISA) for serum anti-aprotinin IgE. These data were extracted when available.

Median age with range is reported for this cohort. Incidence of reactions was calculated for early (within 1 year) versus late (greater than 1 year) re-exposure groups, and for patients at first and subsequent re-exposures and expressed as absolute percentage with binomial exact 95\% confidence intervals (CI) (Stata 10.0, College Station, TX, USA). Likelihood ratio and exact chi-squared tests were used to compare the incidence of a systemic hypersensitivity reaction between the groups.

3. Results

From March 1994 through June 2007, there were a total of 2333 aprotinin exposures in 1824 surgical patients. Median patient age was 9.4 months (range 0 days to 42.6 years). Within this cohort, there were 509 aprotinin re-exposures in 381 patients. Median age at re-exposure was 20.9 months (range 4 days to 21.1 years). A total of 280 re-exposures occurred in 244 patients within the early group and 229 re-exposures occurred in 222 patients within the late group (Fig. 1). The median age of patients in the early re-exposure group was 4.7 months (range 4 days to 19.9 years) compared with 39.4 months (range 12.5 months to 21.1 years) in the late group.

In the 509 aprotinin re-exposures, 19 hypersensitivity (local and systemic) reactions (3.7\%) were observed in 18 patients (median age 30.0 months, range 3.4 months to 18.7 months).
years). The interval between exposures and the incidence of hypersensitivity are illustrated in Fig. 2. Eight of the 19 reactions occurred with skin testing. Eleven of the 19 reactions occurred during aprotinin infusion. There were no reactions with the aprotinin intravenous test dose.

Of the 19 hypersensitivity reactions, six were local skin reactions (Table 1) and 13 were systemic reactions (Table 2) as previously defined. The six patients who had pre-incision positive skin tests resulting in local reactions had aprotinin re-exposure within 1 year of prior exposure. None of the six patients with local reactions alone developed systemic symptoms. Four of these six patients received intravenous aprotinin without systemic reaction. The incidence of local only reaction was significantly higher in the early re-exposure group compared with the late group: 2.1% (CI 0.8–4.6%) versus 0% (CI 0–1.6%), \( p = 0.019 \).

Thirteen systemic hypersensitivity reactions occurred in the 509 re-exposures (2.6%): two during the skin test and 11 during aprotinin infusion. Six reactions occurred in 280 early re-exposures versus seven reactions in 229 late re-exposures (Table 3). None of the 11 patients that had systemic reactions during aprotinin infusion had a positive skin test or a positive intravenous test dose (Fig. 1). Five of the six systemic reactions within 1 year of prior exposure occurred within 6 months of the most recent exposure. As many as 224 of the total 280 early re-exposures were within the first 6 months (80%) of the prior exposure. The incidence of systemic reaction for re-exposure within 6 months was 2.2% (CI 0.7–5.1%).

Six of the 18 patients with a local or systemic hypersensitivity reaction with the first re-exposure had an additional (third or fourth) exposure to aprotinin. One of these six patients had a second systemic hypersensitivity reaction with the third exposure.

Systemic hypersensitivity reactions categorised by re-exposure number are summarised in Table 4. The incidence of systemic reactions was not increased in patients with multiple re-exposures (2.6 \( \pm \) 0.8% vs 2.5 \( \pm \) 1.4%; \( p = ns \)).

<table>
<thead>
<tr>
<th>Rxn</th>
<th>Age (days)</th>
<th>Operation</th>
<th>Exposure</th>
<th>Interval (days)</th>
<th>Reaction (timing)</th>
<th>Treatment</th>
<th>Full dose aprotinin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>143</td>
<td>Ross procedure</td>
<td>2nd</td>
<td>45</td>
<td>Hypotension (infusion)</td>
<td>Aprotinin stopped</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>132</td>
<td>Cavopulmonary shunt</td>
<td>2nd</td>
<td>119</td>
<td>Hypotension (infusion)</td>
<td>Epinephrine</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>214</td>
<td>Homograft replacement</td>
<td>2nd</td>
<td>178</td>
<td>Bronchospasm, tachycardia, widened PP (skin test)</td>
<td>Epinephrine</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>280</td>
<td>Cavopulmonary shunt</td>
<td>2nd</td>
<td>238</td>
<td>Hypotension, hypoxia (infusion)</td>
<td>Epinephrine</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>465</td>
<td>Cavopulmonary shunt</td>
<td>3rd</td>
<td>250</td>
<td>Hypotension, local erythema (skin test)</td>
<td>Epinephrine</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>480</td>
<td>Homograft replacement</td>
<td>2nd</td>
<td>299</td>
<td>Hypotension, decreased CVP, flushing (infusion)</td>
<td>Epinephrine, volume, benadryl</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>2306</td>
<td>Fontan</td>
<td>3rd</td>
<td>14</td>
<td>Hypotension, tachycardia, flushing, wheezing (infusion)</td>
<td>Ephedrine, phenylephrine</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>6817</td>
<td>Aortic valve replacement</td>
<td>2nd</td>
<td>57</td>
<td>Hypotension (infusion)</td>
<td>Epinephrine</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>137</td>
<td>Ventricular septal defect closure</td>
<td>2nd</td>
<td>86</td>
<td>Bronchospasm, tachycardia, widened PP (skin test)</td>
<td>Epinephrine</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>101</td>
<td>Cavopulmonary shunt</td>
<td>2nd</td>
<td>91</td>
<td>Hypotension, hypoxia (infusion)</td>
<td>Epinephrine</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
<td>1155</td>
<td>Lung decortication</td>
<td>3rd (2nd rxn for this pt., see rxn 13)</td>
<td>171</td>
<td>Hypotension, local erythema (skin test)</td>
<td>Epinephrine</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td>200</td>
<td>Supravalvular stenosis repair</td>
<td>2nd</td>
<td>189</td>
<td>Hypotension, tachycardia, flushing, wheezing (infusion)</td>
<td>Ephedrine, phenylephrine</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
<td>984</td>
<td>Fontan</td>
<td>2nd</td>
<td>682</td>
<td>Hypotension, tachycardia, erythema (infusion)</td>
<td>Epinephrine</td>
<td>Yes</td>
</tr>
<tr>
<td>14</td>
<td>899</td>
<td>Fontan</td>
<td>2nd</td>
<td>777</td>
<td>Hypotension, hypoxia (infusion)</td>
<td>Epinephrine</td>
<td>No</td>
</tr>
<tr>
<td>15</td>
<td>1113</td>
<td>Fontan</td>
<td>2nd</td>
<td>962</td>
<td>Hypotension (infusion)</td>
<td>Epinephrine</td>
<td>Yes</td>
</tr>
<tr>
<td>16</td>
<td>1109</td>
<td>Fontan</td>
<td>3rd</td>
<td>1013</td>
<td>Hypotension, decreased CVP, flushing (infusion)</td>
<td>Epinephrine, volume, benadryl</td>
<td>Yes</td>
</tr>
<tr>
<td>17</td>
<td>1514</td>
<td>Frontal orbital advancement</td>
<td>2nd</td>
<td>1098</td>
<td>Hypotension, hypoxia, tachycardia (infusion)</td>
<td>Epinephrine, benadryl, solucortef</td>
<td>No</td>
</tr>
<tr>
<td>18</td>
<td>6415</td>
<td>Aortic root reconstruction</td>
<td>2nd</td>
<td>1408</td>
<td>Hypotension, hypoxia, tachycardia (infusion)</td>
<td>Volume, benadryl, zantac</td>
<td>Yes</td>
</tr>
<tr>
<td>19</td>
<td>4236</td>
<td>Ventricular septal defect closure</td>
<td>2nd</td>
<td>2631</td>
<td>Hypotension, decreased CVP (infusion)</td>
<td>Epinephrine, dopamine</td>
<td>No</td>
</tr>
</tbody>
</table>
Table 3
Systemic hypersensitivity by re-exposure interval.

<table>
<thead>
<tr>
<th>Re-exposure interval</th>
<th>Events (n)</th>
<th>Re-exposures (n)</th>
<th>Incidence rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>13</td>
<td>509</td>
<td>2.6% (1.4% to 4.3%)</td>
</tr>
<tr>
<td>Late (&gt;1 year)</td>
<td>7</td>
<td>229</td>
<td>3.1% (1.2% to 6.2%)</td>
</tr>
<tr>
<td>Early (&lt;1 year)</td>
<td>6</td>
<td>280</td>
<td>2.1% (0.8% to 4.6%)</td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td></td>
<td>0.8% (−1.9% to 3.7%)</td>
</tr>
</tbody>
</table>

p: ns (likelihood ratio).

Aprotinin-specific IgE levels were obtained after nine of the 19 reactions. IgE levels were obtained at the time of five systemic and four isolated skin hypersensitivity reactions. The patient who had two hypersensitivity reactions, one with second exposure and one with third exposure, was the only patient to have a positive IgE titre. It was positive only after the second reaction (third exposure).

Of the 13 patients with systemic hypersensitivity reactions, 11 required interventions with an intravenous sympathomimetic agent, most commonly epinephrine, because significant cardiovascular and/or pulmonary dysfunction heralded the systemic hypersensitivity reaction (Table 2). All patients responded to the supportive measures and no patient had to be resuscitated by going on cardiopulmonary bypass emergently. Five of these patients continued to receive aprotinin throughout the procedure and did not develop any recurrent systemic symptoms (Table 2). In all cases, the scheduled operation was completed as planned.

4. Discussion

Safety of aprotinin during paediatric cardiac surgery has only been profiled in multiple retrospective and observational studies. In summary, reported adverse events in children exposed to aprotinin use is low. The most common adverse event reported in congenital heart surgery is hypersensitivity following primary or secondary exposure with a reported incidence of 1−3% [8–10]. In a series of adults and children who received aprotinin during cardiac surgery, Dietrich et al. reported a 0.2% incidence of hypersensitivity to primary exposure to aprotinin and a 1.5% incidence during secondary exposure. The incidence in the subset of patients undergoing congenital heart surgery was 0.1% with primary exposure and 1.5% with secondary exposure. Re-exposure to aprotinin within 6 months, between 6 and 12 months and greater than 12 months of the previous exposure was associated with a 4.1%, 1.9% and 0.4% incidence of hypersensitivity for the entire cohort, which suggested a strong temporal relationship between hypersensitivity and recent re-exposure [7]. Similar findings by Beierlein et al. also concluded that hypersensitivity reactions were more frequent at shorter re-exposure intervals [11]. These findings led to the FDA black box warning for aprotinin listing re-exposure within a year of prior exposure as a contraindication to use. This warning led to our comprehensive review of aprotinin re-exposure at the Children’s Hospital of Wisconsin. This study marks the largest series of aprotinin re-exposure in paediatric surgery to date.

In this series of 509 aprotinin re-exposures, there were a total of 19 (3.7%) hypersensitivity reactions: six (1.2%) were local skin reactions (erythema and/or swelling) and 13 (2.6%) were systemic reactions. We investigated the temporal relationship between the systemic hypersensitivity reactions and the interval between aprotinin exposures (Table 3). In contrast to findings by others [7,11], the incidence of a systemic hypersensitivity reaction was not increased with early re-exposure. Similarly, we did not find evidence of increased incidence of systemic hypersensitivity with multiple re-exposures. Clinically relevant differences between groups could be excluded based on 95% confidence intervals.

None of the patients with isolated cutaneous reactions had systemic hypersensitivity, including the four patients who were administered aprotinin following the positive skin test, highlighting the negative predictive value of the aprotinin skin test. Only one patient had detectable aprotinin-specific IgE levels; this was observed after a second systemic hypersensitivity reaction (third exposure to aprotinin). Similarly to previous reports the predictive value of antibody tests to identify those patients at risk for hypersensitivity appears limited [5,12,13]. The lack of correlation between tests and clinically relevant systemic reactions to aprotinin may partly be related to our operational definition of hypersensitivity in the current and other case series. Specifically, if hypersensitivity was defined as clinical manifestation of systemic side effects in the presence of antibody-specific antibodies, this study and other series likely overestimated the incidence of aprotinin-induced hypersensitivity or anaphylactoid reactions.

The retrospective design of the data analysis and post hoc definition of systemic hypersensitivity may contribute to imprecision in the estimate of incidence of systemic hypersensitivity to aprotinin. Many patients have vasodilation and relative hypotension during aprotinin infusion without having other manifestations of an anaphylactoid reaction. We chose to include these patients even in the absence of documented skin and respiratory manifestations because we could not rule out a true absence of symptoms versus a deficiency in documentation, a limitation of this study. The mechanism of these vasodilatory effects may not be immunologic and may obfuscate the incidence of potentially life-threatening anaphylactoid events. Patients experiencing relative hypotension without other manifestations of anaphylactoid reactions were not intended to be included as hypersensitivity reactions in this report, and we suspect that some of the systemic reactions reported herein and elsewhere have biologically heterogeneous mechanisms. The increased incidence of local but not systemic reactions with early re-exposure, and the lack of systemic reaction to high dose intravenous aprotinin administered following local
reaction to skin test, suggests that immunologic mechanisms are not responsible for a significant proportion of systemic reactions.

In this series, the apparent incidence of hypersensitivity to aprotinin upon re-exposure is similar to the previous reports in adults and children, in the range of 1—4% [6—9]. However, in contrast to previous reports and to the black box warning issued by the FDA, the incidence of a systemic hypersensitivity reaction was not increased when re-exposure occurred within 1 year or even within 6 months of the previous exposure as compared with those patients re-exposed more than 1 year from the previous exposure. In general, the incidence of a systemic or anaphylactoid reaction was less than 3% and was responsive to sympathomimetic therapy. Because the incidence of these reactions was not increased by recent prior exposure or multiple re-exposures, we question the immunologic basis for these reactions, and the basis for the FDA black box warning. Our own experience [14] suggests that the reported risk of systemic, manageable, non-fatal hypersensitivity to aprotinin is acceptable when considering the use of aprotinin in high-risk paediatric patients undergoing cardiac surgery requiring cardiopulmonary bypass. A prospective risk—benefit analysis of aprotinin use in complex paediatric cardiac surgery from randomised studies is warranted; however, its current orphan status and the unavailability for clinical or research purposes hinders the ability to properly study aprotinin in infants and children.

References


Appendix A. Conference discussion

Dr M. Wojtalik (Poznan, Poland): There is numerous literature on aprotinin properties and adverse reaction after its administration. Immune response and aprotinin administration causes anaphylactic reaction in some patients mainly during second or consecutive treatment. This problem was studied by several authors analysing data collection from mixed adult and paediatric groups.

The presented paper concentrates on the large 381 paediatric group. This retrospective analysis fills the gap of our knowledge about incidents of hypersensitivity reactions after aprotinin readministration in children. Collected data put the proper proportion to the problem.

There were a few weak points of this analysis. The first, it is a retrospective study where there was no constant protocol of reaction in given situations. For example, in some positive skin tests or even systemic reaction, the therapy was continued, or in some other patients was discontinued. Also, immune test was performed only on a few patients, so it is difficult to derive any conclusion out of these few tests. In fact, we don’t know that much, or almost nothing, about the nature of the reaction.

I have two questions.

Readministration of aprotinin took place after 4 days to 21 years, according to your manuscript. Don’t you think that the 2-week delay from first administration should be considered as a second administration or readministration because of the immune system physiology?

And second: do you think that benefits from aprotinin infusion outweigh the risk of continued treatment even in the presence of adverse systemic reaction or a positive skin test? Even we know from literature that some fatal complications after aprotinin administration exist?

Dr Siehr: To address your first question of having a hypersensitivity reaction with a 2-week delay, we did not take that into account. We wanted to look at all of the re-exposures. As you said, the shortest re-exposure interval was 4 days after primary exposure. Because we did not know the nature of the reaction, we wanted to look at all the re-exposures not just after 2 weeks.

To address your second question, each case was decided on a case-by-case basis and the risk and benefits of continuing aprotinin therapy despite an adverse reaction were weighed in the operating room by the anaesthesiologist and the surgeon in the determination of whether or not to continue aprotinin infusion or restart it. In general, if the adverse event was transient and self-limiting in nature or promptly responded to simple interventions such as transient interruption of the infusion, volume or small doses of catecholamines the team typically decided to quickly re-expose the patient to aprotinin. If reactions were severe or protracted and the patient showed prolonged haemodynamic or respiratory instability aprotinin was not restarted. Definitely the risk and benefit was carefully weighed in each case. And in each case of restarting aprotinin we did not see any further reaction when the aprotinin was continued.