

An Anaphylactic Reaction After Primary Exposure to an Aprotinin Test Dose in a Child With a Severe Milk Allergy

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ANAPHYLACTIC REACTION to aprotinin is usually seen after previous exposure to the drug and is rarely seen on primary exposure.¹⁻⁴ There is only one previous case report describing a severe anaphylactic reaction after primary exposure to aprotinin with a positive aprotinin-specific immunoglobulin (Ig) E.⁵ However, Beierlein et al,⁶ in a letter to the editor, raised doubts concerning the interpretation of this case report by stressing that the presence of aprotinin-specific IgE means presensitization, and, hence, such a reaction cannot be considered a primary exposure.

The authors report the first case of an anaphylactic reaction after primary exposure to a test dose of aprotinin in a child with a history of severe milk allergy. Cross-sensitization may occur between milk and aprotinin, which is derived from bovine origin. Blood testing of the patient revealed negative aprotinin-specific IgE antibodies, whereas it was positive for aprotinin-specific IgG4 antibodies, which are used as a screening test for food hypersensitivity.

CASE REPORT

A 9-year-old boy with a history of severe milk allergy was scheduled for placement of a right ventricular-to-pulmonary artery conduit and aortic valve replacement. The patient was born with truncus arteriosus type II and underwent a Rastelli procedure when he was 1 month old. At 1 year of age, he underwent relief of right-ventricular outflow tract obstruction by using a pericardial patch.

During the present surgery, an aprotinin test dose of 1 mL containing 10,000 KIU was injected intravenously after sternotomy. Immediately after injecting the test dose of aprotinin, the patient developed severe hypotension associated with an increased airway pressure. Systolic blood pressure dropped from 120 mmHg to 50 mmHg and remained low for 30 minutes, despite the intravenous administration of repeated doses of epinephrine and 500 mL of 5% albumin. In addition, the patient received a 400-mL bolus of lactated Ringer's solution, and a continuous epinephrine infusion was started.

Cardiopulmonary bypass (CPB) was rapidly initiated after heparinization. On bypass, the patient's mean arterial pressure was initially 15 to 25 mmHg and was increased within 15 minutes to 45 mmHg. A tryptase level while on CPB was 59.2 µg/L (normal 11.5 µg/L).

The surgery continued uneventfully. The patient was weaned from CPB using inotropic support and was transferred to the intensive care unit. On postoperative day 2, inotropic support was discontinued. One week later, the child was discharged home without any evidence of neurologic sequelae. Postoperative immunologic enzyme-linked immunosorbent assay testing showed a negative test for latex allergy, a negative aprotinin-specific IgE titer, and a positive aprotinin-specific IgG4 titer.

During preoperative evaluation of the child, the mother had mentioned that her child was allergic to milk. On further questioning after

the event, the mother revealed that, since birth, her child was diagnosed as having milk intolerance and was put on formula. At the age of 1.5 years, while eating ice cream containing milk, the patient developed a severe allergic reaction, with tachycardia, tachypnea, vomiting, and severe lethargy. These symptoms lasted for 2 to 3 hours and resolved spontaneously. Immunologic RAST tests at that time confirmed the milk allergy.

DISCUSSION

Aprotinin is a serine protease inhibitor, reducing kallikrein, plasmin, and trypsin activity.³ It has antifibrinolytic, anti-inflammatory, and platelet preserving effects. Aprotinin is a 58 amino-acid protein extracted from the bovine lung. It is immunogenic and severe allergic reactions occur mainly after reexposure. The incidence of aprotinin anaphylaxis with reexposure has been reported as 2.8%¹ to 17%.² However, reviewing this patient's old chart showed that he did not receive aprotinin during his 2 previous surgeries. Furthermore, he did not receive any biologic tissue sealants that contain aprotinin that may be used during cardiac surgery.^{7,8} Tissue sealants have been commercially available in the United States since 1998. This patient underwent 2 previous surgeries in 1994 and 1995, before the availability of aprotinin-containing tissue sealants.

In the present surgery, the patient developed a severe anaphylactic reaction after primary exposure to an aprotinin test dose (10,000 KIU). During CPB, the tryptase level was high. Tryptase is released from mast cells only and provides a more specific marker than histamine for anaphylaxis.⁹ Postoperatively, blood testing revealed negative aprotinin-specific IgE, which eliminates the possibility of previous exposure to aprotinin. However, it was positive for aprotinin-specific IgG4 antibodies, which are used as a screening test for food hypersensitivity.¹⁰

Aprotinin-specific IgE may become detectable 1 week after primary aprotinin contact. IgG4 antibodies have been reported

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1053-0770/07/2102-0014\$32.00/0

doi:10.1053/j.jvca.2006.03.001

Key words: anaphylaxis, aprotinin, immunoglobulin G4 (IgG4), milk allergy, pediatrics, cardiac surgery

in patients with eczema and/or asthma caused by milk intolerance. Also, IgG4 antibodies were reported in patients with atopic dermatitis and/or bronchial asthma caused by soy bean hypersensitivity. Serum IgG4 antibody testing to common food antigens is being offered as a screening test for food hypersensitivity.¹⁰ Some patients who have used exclusion diets based on elevated IgG4 titers have reported improvement in their symptoms. The reaction to aprotinin thus may be attributed to the history of severe milk allergy as confirmed by clinical symptoms and by immunologic RAST tests. Because aprotinin is a derivative of bovine lung, the patient might have developed anaphylaxis to aprotinin secondary to cross-sensitization with milk. Cross-sensitization may occur with other bovine products such as beef, egg white, and cheese.¹¹ This complication is similar to the cross-sensitization between protamine, a salmon sperm derivative, and salmon.¹²

In conclusion, the first case is reported of an anaphylactic reaction after primary exposure to an aprotinin test dose in a child with a history of severe milk allergy. The child was negative for aprotinin-specific IgE, which eliminates the pos-

sibility of previous exposure to aprotinin. However, he had positive aprotinin-specific IgG4 antibodies, which are often elevated with a food allergy. The authors believe that this reaction may be secondary to cross-sensitization between aprotinin, a bovine lung derivative, and milk. It is recommended that special attention be given when administering aprotinin to a patient with an allergy to milk and/or other bovine products. The author's group will not use aprotinin in a patient with severe milk allergy in the future, even if not exposed to aprotinin in the past. The benefit of using aprotinin versus the risk of an adverse event in such cases is left to the clinician's judgment.

ACKNOWLEDGMENT

The authors would like to thank Dr Michael Zacharisen, Assistant Professor of Pediatrics and Medicine (Allergy and Immunology), Medical College of Wisconsin, Milwaukee, WI, for his contribution in performing the immunologic enzyme-linked immunosorbent assay testing for latex allergy, aprotinin-specific IgE titer, and aprotinin-specific IgG4 titer.

REFERENCES

1. Beierlein W, Scheule AM, Dietrich W, et al: Forty years of clinical aprotinin use: A review of 124 hypersensitivity reactions. *Ann Thorac Surg* 79:741-748, 2005
2. Dietrich W, Spath P, Ebell A, et al: Prevalence of anaphylactic reactions to aprotinin: Analysis of two hundred forty-eight reexposures to aprotinin in heart operations. *J Thorac Cardiovasc Surg* 113:194-201, 1997
3. Milano CA, Patel VS, Smith PK, et al: Risk of anaphylaxis from aprotinin re-exposure during LVAD removal and heart transplantation. *J Heart Lung Transplant* 21:1127-1130, 2002
4. Scheule AM, Beierlein W, Lorenz H, et al: Repeated anaphylactic reactions to aprotinin in fibrin sealant. *Gastrointest Endosc* 48:83-85, 1998
5. Cohen DM, Norberto J, Cartabuke R, et al: Severe anaphylactic reaction after primary exposure to aprotinin. *Ann Thorac Surg* 67:837-838, 1999
6. Beierlein W, Scheule AM, Ziemer G: Anaphylactic aprotinin reaction. *Ann Thorac Surg* 69:1298, 2000
7. Scheule AM, Beierlein W, Wendel HP, et al: Fibrin sealant, aprotinin, and immune response in children undergoing operations for congenital heart disease. *J Thorac Cardiovasc Surg* 115:883-889, 1998
8. Scheule AM, Beierlein W, Wendel HP, et al: Aprotinin in fibrin tissue adhesives induces specific antibody response and increases antibody response of high-dose intravenous application. *J Thorac Cardiovasc Surg* 118:348-353, 1999
9. Fisher MM, Baldo BA: Mast cell tryptase in anaesthetic anaphylactoid reactions. *Br J Anaesth* 80:26-29, 1998
10. Bergamaschini L, Santangelo T, Faricciotti A, et al: Study of complement-mediated anaphylaxis in humans. The role of IgG subclasses (IgG1 and/or IgG4) in the complement-activating capacity of immune complexes. *J Immunol* 156:1256-1261, 1996
11. Laxenaire MC, Dewachter P, Pecquet C: [Allergic risk of aprotinin]. *Ann Fr Anesth Reanim* 19:96-104, 2000
12. Knape JT, Schuller JL, de Haan P, et al: An anaphylactic reaction to protamine in a patient allergic to fish. *Anesthesiology* 55:324-325, 1981