

Severe Anaphylactic Reaction After Primary Exposure to Aprotinin

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Aprotinin is widely used to prevent bleeding and reduce blood transfusions after open heart surgical procedures. Because it is a foreign protein, aprotinin has allergenic potential. We report a case of near-fatal anaphylactic reaction to primary aprotinin exposure in a child successfully treated using cardiopulmonary bypass support. The possibility of an allergic reaction must be considered whenever this drug is used.

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In an era where the risks of blood transfusion are of public concern, there is increased impetus to conserve blood and reduce postoperative bleeding. Aprotinin, a protease inhibitor extracted from bovine lung, has been administered intraoperatively in select adult and pediatric patients undergoing open heart surgical procedures deemed at high risk for excess bleeding. Its use has been associated with a marked reduction in perioperative blood loss and postoperative transfusion requirements. Because aprotinin is a foreign protein, it has allergenic potential. Allergic or severe anaphylactic reactions have been reported, but mainly with reexposure. A near-lethal reaction to aprotinin on initial exposure is very unusual. Herein we report a severe, anaphylactic reaction to aprotinin in a child immediately after the administration of a test dose, which was successfully treated using cardiopulmonary bypass support.

A 3½-year-old boy underwent complete repair of tetralogy of Fallot with absent pulmonary valve syndrome as a neonate. Aprotinin (Bayer, West Haven, CT) was not used perioperatively. He had done well postoperatively, and except for known bronchomalacia and sporadic episodes of wheezing, he required rare hospital admission and was thriving. He had no known allergies, including beef.

At cardiac catheterization there was an 80-mm Hg gradient across the right ventricular-pulmonary artery conduit. The patient was readmitted for elective replacement of the right ventricular-pulmonary artery conduit. After induction of general anesthesia and intubation, both radial arterial and femoral venous lines were inserted for monitoring purposes. A 1-mL test dose of aprotinin (10,000 KIU) was administered intravenously.

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Immediately his systemic blood pressure became undetectable, and there was an associated sudden increase in peak airway pressures and difficulty maintaining adequate ventilation. Cardiopulmonary resuscitation was initiated. Repeated boluses of epinephrine, sodium bicarbonate, and calcium chloride were administered intravenously. The patient also received intravenous methylprednisolone, diphenhydramine, and cimetidine because of a suspected allergic reaction.

After 50 minutes of continuous cardiopulmonary resuscitation, despite multiple boluses of intravenous epinephrine and the initiation of high-dose epinephrine infusion ($0.3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{mm}^{-1}$), there were no signs of recovery of cardiac function. Cardiopulmonary bypass was instituted by direct cannulation of the femoral artery and vein, and the patient was allowed to recover. As he began to show evidence of pulsatile arterial blood flow, he was slowly weaned off inotropic support, and cardiopulmonary bypass was discontinued after 73 minutes. The patient was transferred to the pediatric intensive care unit, where he underwent intubation and ventilation with infusions of epinephrine ($0.08 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{mm}^{-1}$) and sodium nitroprusside ($2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{mm}^{-1}$). He recovered from general anesthesia without any evidence of neurologic sequelae. He was weaned off inotropic infusions, and they were discontinued by postoperative day 2.

During his stay in the pediatric intensive care unit, specimens of the patient's blood and a sample of aprotinin from the pharmaceutical vial were sent for enzyme-linked immunosorbent assay (ELISA). He had highly elevated IgE levels in response to aprotinin. A latex radioallergosorbent test was also performed, but no IgE levels in response to latex were detected. Protamine, a common cause of life-threatening reactions during cardiac operation, had been administered at the time of the patient's neonatal repair but had not been given before signs of cardiovascular collapse during this operation. Furthermore, the patient did not react to protamine when it was administered at the termination of cardiopulmonary bypass.

The patient was discharged from the hospital in satisfactory condition, without any evidence of neurologic sequelae. He returned 3 months later for the replacement of the right ventricular-pulmonary artery conduit. He tolerated this procedure well, without any adverse reaction to protamine and was discharged home on the fifth postoperative day. He has remained neurologically normal over the past 8 months.

Comment

Blood conservation and the prevention of bleeding after open heart surgical procedures are of intense concern to both health care professionals and the public at large. Any method that can avoid or decrease allogenic blood transfusions will decrease the risks of contracting blood-borne diseases. Aprotinin is a protease inhibitor that influences complement activation and the coagulation and fibrinolytic pathways. Its use has been reported to result in a 30% to 40% reduction in perioperative blood loss and transfusion requirements [1]. Aprotinin has proved particularly useful in patients undergoing reoperation. Because this protein is derived from bovine lung

tissue, it has antigenic risks. Approximately 50% of all patients exposed to aprotinin form detectable IgG immunoglobulins within 3 months of exposure [2]. With larger numbers of patients who are receiving aprotinin and undergoing subsequent cardiac operations, the incidence of reexposure is increasing. This group is known to be vulnerable to hypersensitivity reactions; however, the prevalence of adverse drug reactions to aprotinin reexposure has been reported to be only 2% to 4% [3]. These reactions are usually mild and manifest typically with a skin rash. An immediate type of allergic reaction involving IgE immunoglobulins directed against aprotinin has been described but usually in response to previous exposure [4]. The overall risk of anaphylactoid reactions to aprotinin is estimated to be 0.5% [5]. Typically, when this reaction occurs, the vascular system is initially refractory to high-dose catecholamines, and blood pressure can only be maintained by vigorous, prolonged cardiopulmonary resuscitation, and this condition may be fatal. Our patient did not recover after conventional and prolonged cardiopulmonary resuscitation; he was resuscitated only after prolonged cardiopulmonary bypass (73 minutes).

Fatal or near-fatal outcomes in response to primary exposure to aprotinin are exceedingly unusual. A case report documenting adult respiratory distress syndrome in a young adult in response to primary aprotinin exposure has been described [6]. Evidence for an IgE-type reaction in that case is questionable: Symptoms did not manifest until 2 hours after exposure; there were no signs of cardiovascular collapse; and the immunologic study results were normal.

Our case represents a documented report of an immediate, near-fatal response to aprotinin on primary exposure with a documented IgE-mediated immunologic reaction. It raises concern about the safety of aprotinin and begs the question of whether previous epicutaneous testing (prick test) should be undertaken before the administration of an intravenous test dose, even in "virgin" patients. Evidence for the sensitivity and specificity of such testing is lacking. Because the incidence of anaphylactic reactions is rare and occurs mainly in patients with a previous history of exposure, such measures seem excessive. Caution should, however, be exercised with aprotinin administration (even with a test dose), especially in those patients who will be subjected to reexposure.

In light of the rarity of this complication, we recommend that planning for the immediate initiation of cardiopulmonary bypass be undertaken only in patients with a history of previous exposure. Furthermore, the possibility of an allergic reaction should be considered whenever this drug is used.

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Aortic Valve Replacement After Substernal Colon Interposition

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A 60-year-old man with a history of esophageal resection and substernal colon interposition required aortic valve replacement for aortic stenosis. The aortic valve was approached through an 8-cm right parasternal incision over the third and fourth costal cartilages with cardiopulmonary bypass using cannulas in the right femoral artery and vein and the right atrium. The right parasternal approach provided safe exposure of the aorta and left ventricular outflow tract when substernal abnormalities precluded conventional median sternotomy.

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Currently there is great interest in the development of less invasive approaches for operations on the heart and great vessels. In our investigation of alternate incisions for aortic valve replacement, we initially used a right parasternal approach [1]. This incision provides excellent exposure of the aortic root and left ventricular outflow tract. Potential disadvantages of this technique include sacrifice of the right internal thoracic artery, frequent need for femoral cannulation, occasional chest wall instability, and difficult conversion to full sternotomy. Therefore, in most patients we currently approach the aortic valve using an 8-cm midline skin incision and a partial sternotomy extended to the right fourth intercostal space. In the present report, we describe a case in which the right parasternal approach provided safe exposure of the aortic valve in a patient who could not have median sternotomy.

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