Fatal anaphylactoid reaction after primary exposure to aprotinin

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Received 22 August 2005; received in revised form 17 October 2005; accepted 19 October 2005

Abstract

Aprotinin is widely used to prevent bleeding, inhibit systemic inflammatory response and reduce blood transfusions after cardiac surgery. Because it is a bovine protein, aprotinin can induce hypersensitivity reactions. We report a case of fatal anaphylactoid reaction to primary aprotinin exposure in a woman who was admitted for mitral valve replacement. The possibility of anaphylactic reaction should be considered whenever aprotinin is used.

Keywords: Surgery complications; Surgery emergency; Resuscitation

1. Introduction

Antifibrinolytic agents play a prominent role in adult cardiac surgery. Cardiopulmonary bypass induces a set of complex imbalances in the haemostatic systems, which can result in coagulopathy, postoperative bleeding and increase transfusion requirements. Aprotinin (Trasylol, Bayer Corporation) is the most potent antifibrinolytic agent that attenuates inflammatory responses and reduces blood transfusion. Because aprotinin is a foreign protein, it has allergenic potential. Forty-one cardiac surgery patients with induced adverse reactions have been reported, but mainly with reexposure. We report a lethal reaction to aprotinin without former aprotinin exposure, which is very unusual.

2. Case report

A 74-year-old woman had a history compatible with acute rheumatic fever during adolescence. She did well during 30 years until progressive symptoms of congestive heart failure appeared, coinciding with the onset of chronic atrial fibrillation. An echocardiogram showed severe mitral regurgitation with moderate stenosis (1.2 cm²) and severe tricuspid regurgitation with pulmonary hypertension (52 mmHg). Left ventricular ejection fraction was 60%. Coronary angiography did not show coronary disease. With this diagnosis, the patient was admitted for elective mitral valve replacement and tricuspid annuloplasty. The patient had not any known allergy against food or drugs. Despite a previous bilateral hallux valgus surgery, the possibility of aprotinin contamination was unlikely.

Pressures were monitored and after induction of general anaesthesia and intubation, a test dose of aprotinin (10,000 KIU) was administered intravenously, according to our policy in order to reduce inflammatory responses and bleeding, even in first cardiac operations. In that moment, neither colloid infusions nor antibiotic prophylaxis, were being administered. Immediately, her systemic blood pressure became undetectable, there were urticarial lesions in the skin and associated increase in peak airway pressure, with atrial fibrillation (electromechanical dissociation). Cardiopulmonary resuscitation was initiated. Repeated bolus of methoxamine, epinephrine, norepinephrine and calcium chloride were administrated intravenously. In view of the possibility of an allergic reaction, the patient also received methylprednisolone, diphenhydramine and cimetidine. After 20 min of continuous cardiopulmonary resuscitation, despite multiple bolus and high-dose infusion (0.5 μg kg⁻¹ min⁻¹) of epinephrine, there were no signs of recovery of cardiac function, with refractory ventricular fibrillation probably due to ischemia. An emergent median sternotomy was performed and cardiopulmonary bypass was instituted by cannulation of the ascending aorta and right atrium, venting the left ventricle through the right superior pulmonary vein. After 120 min of cardiopulmonary support, the vascular system was still refractory and the patient was not weaned off cardiopulmonary bypass despite high-dose catecholamines infusions and intraaortic balloon pump.

During this time, specimens of the patient’s blood were sent to the laboratory. She had highly elevated tryptase levels (200 μg/l), IgE and histamine were not detected, and complement levels were low (C3 convertase 23 mg/100 ml, C4 5 mg/100 ml). We could not obtain ELISA results for aprotinin-specific IgE.

3. Discussion

Several pharmacologic approaches to reduce bleeding and transfusion requirements in cardiac surgery patients are
based on either preventing or reversing the defects associated with cardiopulmonary bypass-induced coagulopathy [1]. Blood transfusion exposes patients to infectious diseases as well as an increased risk of postoperative infection. Reexploration for bleeding is associated with an increased risk of atrial arrhythmias, sepsis, respiratory complications, prolonged hospital stay, renal failure and mortality.

In that respect, aprotinin is the most potent antifibrinolytic agent with multiple anti-inflammatory effects [2,3]. Because it is a bovine protein, it has antigenic risk. Although primary exposure to aprotinin is quite safe, reexposure carries a significant risk of adverse reactions. In a recent review, 80% of patients with adverse events had had previous exposure to aprotinin. The risk of anaphylaxis is approximately 2.8% in reexposed patients, most of them occurred within three to six months after primary administration [4]. Hypersensitivity reactions led to severe complications since more than half were life-threatening and 9% were fatal.

Anaphylaxis after primary exposure to aprotinin is rare. Cohen and coworkers have described a similar case [5] in a 3.5-year-old boy with a near-fatal reaction to a test dose of aprotinin administered intravenously before complete surgical repair of tetralogy of Fallot. Although we think that in our patient the management of the situation was correct, with emergent and prolonged cardiopulmonary bypass, we were not able to save the patient's life.

As we can exclude in our case the possibility of former local aprotinin contacts by fibrin tissue adhesives or cross-sensitization, and the formation of specific IgE antibodies anaphylactic reactions requires prior immunologic sensitization, the adverse reaction would not have been IgE mediated and thus not anaphylactic. Anaphylactoid reactions are clinically indistinguishable from anaphylaxis. However, this consideration does not rule out aprotinin from being the causative agent, because there is still the possibility of an antibody-independent anaphylactoid reaction, probably due to a complement activation [6].

Despite the rarity of this complication, an allergic reaction should be considered whenever aprotinin is used. In patients with previous exposure, especially within at least six months, evaluation of aprotinin-specific serum-IgG by commercially screening a test before reexposure would be helpful, because absence of aprotinin-specific IgG indicates a low risk of a hypersensitivity reaction due to its excellent negative predictive value [7].

After this case, we routinely use tranexamic acid as the antifibrinolytic agent in all patients.

**References**


**Appendix A. ICVTS on-line discussion**

**Author:** Michael C. Sinclair (Lehigh Valley Hospital, Allentown, PA, USA)

**eComment:** We also have had a fatal reaction to aprotinin after a ‘negative’ response to a test dose. In the early era of aprotinin use, one patient had reexposure within six months. There was no adverse response to the test dose but fatal anaphylaxis after the full dose. Does anyone know the predictive value of the standard ‘test dose’ of aprotinin?