

Severe anaphylactic shock due to repeated application of aprotinin in patients following intrathoracic aortic replacement

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Abstract. Aprotinin is known to significantly reduce the incidence of perioperative bleeding complications in cardiac, thoracic and vascular surgery. Despite the wide use of this medication in other surgical fields, there are only a few reports of serious adverse side effects. In this paper we report on two patients with severe anaphylactic shock due to repeated administration of aprotinin, who both required cardiopulmonary resuscitation. [Eur J Cardio-thorac Surg (1993) 7:495–496]

Key words: Aprotinin – Anaphylactic shock – Aortic dissection – Cardiopulmonary resuscitation

In the past, various studies have proven the ability of aprotinin to reduce the incidence of perioperative bleeding in cardiac, thoracic and vascular surgery [1, 3]. These data correlate well with our own experience and we have therefore used aprotinin routinely according to the dosage recommended by Royston in patients undergoing cardiac or thoracic aortic surgery [9]. Between 1989 and 1992 a total of 2296 patients, aged 14 or older, received aprotinin, including 48 patients requiring reoperation, who therefore received aprotinin more than once.

To our knowledge, so far there has only been one report in the current literature of a severe allergic reaction due to aprotinin in cardiac surgery [2]. We would therefore like to add our experience with this severe side effect after repeated administration of aprotinin.

Case 1

On November 6, 1990, a 56-year-old female patient had undergone replacement of the ascending aorta with reconstruction of the aortic root for type A aortic dissection. In the preoperative anesthesiologic consultation the patient denied having any history of allergic reactions. The intraoperative anesthesia was unremarkable and the medication included thiopental, pancuronium, fentanyl, cefazolin (two doses, 2 g after induction of anesthesia and 2 g after weaning from cardiopulmonary bypass), calcium and aprotinin, the latter given in a single dosage of 3.5 million KIU. The postoperative occurrence of multiple venous thrombi (left axillary and femoral

veins), leading to swelling and a suspected pulmonary embolization, required additional surgical intervention with a thrombectomy of the left femoral vein. The intraoperative medication for this procedure included cefazolin.

On April 17, 1991, the patient was admitted to our hospital, this time due to a chronic dilatation of the dissected descending aorta. Following placement of an intraarterial cannula for on-line pressure measurement, anesthesia was induced with 350 mg thiopental, 8 mg pancuronium and two doses of 0.5 mg fentanyl. The patient was intubated with a double lumen endotracheal tube and ventilated with 100% oxygen. In addition, one peripheral venous line was inserted on the dorsum of the right hand and one central venous line via the left internal jugular vein. At this time the blood pressure was 140/60 mmHg and the heart rate 80 bpm. Cefazolin was then administered without any evidence of an allergic reaction and 2 million KIU aprotinin were given via the central line within 10 min. At the end of the infusion a remarkable erythema of the upper thorax was noted and subsequently the blood pressure dropped to 90/40 mmHg. An injection of 4 g calcium was without any effect, the erythema now extending over the entire body with isolated urticarial wheals while the heart rate dropped to 30 bpm (sinus bradycardia) and the blood pressure continued to drop to 30/10 mmHg. The initiation of closed chest cardiac resuscitation resulted in an adequate blood pressure of 80/40 mmHg and the heart rate normalized to 100 bpm. In addition the patient received 1500 ml Ringer's lactate, 500 ml gelatin solution, 1.5 g prednisolone, 2 mg clemastin (anti-histamine) and norepinephrine in a total dose of 1 mg. After 20 min of resuscitation the blood pressure was stable at 110/70 mmHg with a heart rate of 90 bpm. It was decided to defer surgery, so the double lumen tube was removed and a single lumen endotracheal tube was inserted and the patient was transferred to the intensive care unit (ICU) for further monitoring. From there she was discharged the next day.

On April 25, 1991, the replacement of the descending aorta was performed without any complications, this time without the administration of either cefazolin or aprotinin. For postoperative antibiotics coverage, cefotaxime was used.

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Case 2

On May 14, 1991, a 17-year-old male patient with Marfan syndrome underwent thoracic aorta replacement and elephant trunk insertion for a chronic type B aortic dissection and thoracoabdominal aneurysm. The patient denied having any history of allergic reactions. During anesthesia 4 g cefazolin and 3.5 million KIU aprotinin were infused without any complications.

On July 18, 1991, replacement of the thoracoabdominal aorta was planned. For induction of anesthesia the patient received 500 mg thiopental, 8 mg pancuronium, 0.5 mg fentanyl as well as 100 mg succinylcholine. The patient was intubated with a double lumen endotracheal tube. The blood pressure at this time was 110/60 mmHg with a heart rate of 85 bpm. After insertion of the usual arterial and venous catheters 2 g cefazolin was administered and the patient was transferred to the operating room and turned to the right lateral decubitus position. The blood pressure remained at 100/60 mmHg with a constant heart rate.

Aprotinin was administered through the central line according to the protocol of case 1. When 750,000 KIU had been infused an erythema of the thoracic region was noted and the infusion was immediately stopped. At this time the blood pressure dropped to 90/40 mmHg and a sinus tachycardia of 150 bpm was noted. Despite the injection of 2×2 g calcium the blood pressure continued to decrease to 40/20 mmHg and the patient was turned on to his back in order to start mechanical cardiac resuscitation. Ventilation was performed with 100% oxygen, and epinephrine and norepinephrine were infused. The patient then received 1500 ml Ringer's lactate and 1000 ml hydroxyethyl starch solution. After 20 min of resuscitation the circulation was stable (BP 100/40 mmHg, HR 140 bpm). At this time a total of 1 mg epinephrine and 9 mg norepinephrine had been administered. Without catecholamines the blood pressure then remained stable at 110/50 mmHg and the heart rate at 140 bpm. Following the decision to defer surgery, the patient was reintubated with a single lumen endotracheal tube and transferred to the ICU for further monitoring. A day later the patient was discharged from this unit.

Without the use of aprotinin but with infusion of 2 g cefazolin the patient underwent uncomplicated elective replacement of the thoracoabdominal aorta on July 22, 1991.

Discussion

Aprotinin is a polypeptide with a molecular weight of 6512 Daltons, which is purified from cattle lung or other tissue [10]. Its effectiveness as a protease inhibitor has been proven with respect to plasmin, kallikrein and kinin [5] and it therefore influences the complement, coagulation and fibrinolytic pathways. In addition, a membrane-stabilizing effect is being discussed as evidenced by an optimization of the thrombocyte membrane function with improvement of thrombocyte aggregation (8), in vitro and in vivo inhibition of the cellular release of histamines [7], as well as a beneficial effect on the thromboxane/prostacycline system [8]. These latter properties may be responsible for the fact that anaphylactic reactions to aprotinin are very rare. In addition, it seems that healthy human beings have a wide physiological tolerance for protease inhibitors with similar specificity [6]. Currently, the incidence of hypersensitive reactions after repeated administration of aprotinin is estimated to be less than 0.1% [4]. The standard administration of aprotinin in our institution has resulted in severe anaphylaxis in 2 of 48 reoperated patients (4.2%).

In these two cases reported the infused antibiotics must be included as potential sources for anaphylaxis.

However, in the first patient the repeated injection of cefazolin had been completed before the occurrence of anaphylactic shock, a fact that clearly reduces the probability of a reaction to cefazolin, while in the other patient all the other medications had been repeatedly administered without causing similar reactions. In addition, we think it important to mention that only cardiac resuscitation was able to improve the blood pressure, while the vascular system initially seemed to be refractory to even high doses of catecholamines.

As a result of these experiences we have become more restrictive concerning the administration of aprotinin. Aprotinin is presently not routinely used in every patient undergoing cardiac or arterial intrathoracic reconstruction, but instead is only employed for reoperations and in patients who have been treated with nonsteroidal anti-inflammatory drugs up to the time of surgery.

Addendum

In the meantime we have experienced three additional patients with anaphylactic shock due to reexposure to aprotinin. Thus, out of 86 patients with repeated aprotinin exposure, a total of 5 (5.8%) have exhibited severe signs of anaphylactic reaction.

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