

Fatal Anaphylactic Shock After Aprotinin Reexposure in Cardiac Surgery

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In open heart surgery, the administration of aprotinin, a proteinase inhibitor extracted from bovine lung, may achieve a 30%–40% reduction in perioperative blood loss and transfusion requirement (1–3). In contrast to all other blood-saving techniques, the use of aprotinin represents a trespass into the patients' immunologic memory. This is why in a recent communication we expressed concern about expanding its use in noncardiac procedures (4). We are now presenting the first report on an anaphylactic shock after aprotinin reexposure in open heart surgery where resuscitation was unsuccessful, even with the aid of cardiopulmonary bypass (CPB).

Case Report

A 31-yr-old patient (49 kg, 146 cm) with a history of abortion 1 yr ago, tonsillectomy 2 mo ago, as well as allergies to gelatin, penicillin, and cephalosporines, was admitted for open commissurotomy of mitral valve stenosis (New York Heart Association class II–III, orifice 0.8 cm², gradient 20 mm Hg, left ventricular end-diastolic pressure 4 mm Hg, pulmonary capillary wedge pressure 30 mm Hg).

Anesthesia was induced intravenously with midazolam, fentanyl, and pancuronium, while the electrocardiogram and invasive arterial blood pressure were monitored continuously. After tracheal intubation, a central venous line was placed via the left internal jugular vein, whereafter an infusion of aprotinin 500,000 Kallikrein inactivation units (KIU) was started via a peripheral vein. Five minutes later, while 250,000 KIU of aprotinin had been infused, the patient's heart rate increased from 70 to 120 bpm, ventilation was impaired by severe bronchospasm, and systolic arterial blood pressure decreased to less than 40 mm Hg. Aprotinin administration was immediately discontinued and external cardiac massage was begun with concomitant administration of epinephrine, methylprednisolone, theophylline, cimetidine, clemastine, and 6% hydroxyethylstarch (1.5 L). Episodes of tachycardia alternated with those of bradycardia until, 10 min after the end of aprotinin administration, asystole ensued, refractory to any further resuscitative efforts,

including esophageal pacemaker. After 40 min it was decided to institute CPB which, after a futile attempt in the groin due to anatomic problems, was performed via sternotomy. With the aid of epinephrine ($0.17 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and dopamine ($5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) satisfactory circulation (arterial blood pressure 90/60 mm Hg, heart rate 85 bpm) was established after a 30-min perfusion, whereafter CPB was discontinued. During CPB blood samples were drawn for antibody testing. On the third day after the event, the patient died from multiorgan failure.

Aprotinin antibodies were determined by means of the immunoblot technique: Out of its pharmaceutical preparation, aprotinin was bound to cellulose nitrate membranes (5) which were incubated sequentially with (i) patient serum (diluted 1:500), (ii) phosphatase-labeled antibodies against human immunoglobulins (IgE and IgG), and (iii) a substrate to give a staining reaction with phosphatase. The resulting color bands were compared with those of reference sera positive and negative for aprotinin-specific IgG. The intensity of the staining reaction was expressed semiquantitatively (–, +, ++, +++). All assays were performed in triplicate. The staining reaction of our patient's serum was negative for fentanyl, pancuronium, and midazolam, ++ for aprotinin-specific IgG, and +++ for IgE.

A review of the patient's previous hospital records obtained after the incident revealed that the tonsillectomy 2 mo before was associated with the administration of two doses of aprotinin 500,000 KIU given 2 h apart with no untoward reaction on record.

Discussion

In Europe, aprotinin has been in clinical use for some 30 yr for a multitude of indications. For the last 10 yr, its indications were centered on its hemostatic effects. Between 1964 and 1993, anaphylactoid reactions to aprotinin have been reported in 26 patients with 3 fatalities. In 9 of these patients, aprotinin was given for acute pancreatitis, in 5 patients during cardiac surgery (6–9), and in the remaining 12 patients for a variety of other indications.

The presence of aprotinin-specific IgG in our patient's serum demonstrates that the present administration of aprotinin represented a reexposure to the drug, a condition unknown preoperatively. Antibodies to aprotinin are highly specific in their affinity to

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the reactive-site region of the protein which represents its major immunogenic epitope (10). There are no known cross-reactions to the immunoblot test for aprotinin-specific antibodies. Thus, in our patient, the anaphylactic shock was related closely to aprotinin administration; the detection of specific IgE antibodies mediating the immediate-type allergic reaction, the immunoblot test negative for the anesthetic drugs administered, and the absence of an antibiotic prove aprotinin as the causative drug.

Our patient's first exposure to aprotinin during tonsillectomy illustrates the risk associated with its indiscriminate use, which usually occurs unrecognized by the patient and remains unsuspected by subsequent physicians. We question the wisdom, as recently published (11), of using aprotinin except in high-risk candidates. Operations where prolonged CPB is not part of the procedure may create unacceptably hazardous conditions and warrant a critical reevaluation of the risk-benefit relation of aprotinin administration for hemostasis.

The manufacturers of aprotinin estimate a 0.5% (i.e., 1:200) overall risk of anaphylactoid reactions. A 0.7% (i.e., 1:143) incidence of untoward events was reported after the first exposure to aprotinin and an up to 9.1% (i.e., 1:11) incidence after reexposure (12,13). Aprotinin reexposure was associated with an almost 6% incidence (5 of 86 patients) of life-threatening (7) conditions as opposed to an overall 1:9000 risk of serious hemolytic reactions per unit of homologous blood transfused (1:176000 lethal) (14). Taking into account the additional incidence of disease transmission [approximately 1:15000 for hepatitis and 1:300000 to 1:3000000 for human immunodeficiency virus (14)], and assuming an average requirement of 4 U of blood per patient (15), adverse effects of homologous blood transfusion may be expected in approximately 1:1300 patients. Hence, untoward effects may be expected at least nine times more often from aprotinin than from homologous blood transfusion. Furthermore, a considerable number of patients, in particular those undergoing reinterventions during the first postoperative days, are exposed to the combined risk of aprotinin and homologous blood transfusion, with the risk unmentioned in the relevant publications.

The effectiveness of high-dose aprotinin administration in reducing perioperative blood loss is best documented in open heart surgery, where an average 35% reduction in blood loss (1037 mL vs 678 mL) and a 53% reduction in transfusion requirement (1999 mL vs 942 mL) have been reported (15). Unfortunately, no one has questioned the increase in the number of patients who, due to aprotinin, could be operated on without any homologous blood transfusion at all—the only pertinent criterion in our opinion. Thus, with the immunologic sequelae in mind, we have difficulty

accepting a mere 500-mL reduction in perioperative blood loss as a basis for routine aprotinin medication.

In our hospital, as an immediate consequence from our incident, we now start an infusion of aprotinin 2,000,000 KIU (3) only after sternotomy, i.e., shortly before the institution of CPB, rather than with induction of anesthesia. In patients with a history of previous exposure to aprotinin, its administration is considered on an individual basis and, after a positive decision, performed under prophylaxis with H₁- and H₂-receptor antagonists. We do not use aprotinin in noncardiac surgery.

In conclusion, both our case report and a brief reappraisal of the literature reveal a clinically relevant risk of serious anaphylactic response on reexposure to aprotinin calling for a thorough reevaluation of the risk benefit-relation. It needs to be shown that the risks conferred by aprotinin are inferior to those of homologous blood transfusion.

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