Severe Intraoperative Anaphylactic Reaction: Aprotinin and Rocuronium

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ANAPHYLACTIC REACTIONS ARE life-threatening situations, with sudden onset, that can happen at any time during anesthesia. Muscle relaxants are the most frequently involved drugs, causing 60% of the intraoperative anaphylactic reactions. Other drugs, like aprotinin, have higher potential to produce an allergic reaction; however, their use is rare compared with the routine use of neuromuscular-blocking drugs (NMBDs).

In the case reported here, a severe anaphylactic reaction occurred after a 1-mL test dose of aprotinin in an adult patient who had a previous exposure to the drug almost 1 year before. There have been other reports of anaphylaxis to aprotinin test doses, but they have occurred in early re-exposures (less than 2 months) and/or when using test doses much larger than recommended. This case suggests the need for other screening tests for anaphylaxis. The allergy workup in this patient revealed sensitization to 2 different drugs: aprotinin, as expected, and, unexpectedly, rocuronium. Therefore, this case also shows that every patient who experiences anaphylaxis must be investigated and advised on future care.

CASE REPORT

A 56-year-old woman (87 kg and 158 cm) previously underwent mitral valve reconstruction to treat mitral regurgitation. Anesthesia was uneventful; the patient received propofol, fentanyl, rocuronium, cefazolin, and aprotinin (Trasylol; Bayer, Leverkussen, Germany) as per the Hammersmith protocol.[1] She had been doing well for 11 months. At that time, the patient experienced clinical deterioration, blood tests revealed hemolysis, and the echocardiogram showed a periannular leak. The patient was readmitted for a new elective mitral valve surgery. She had no known allergies.

On the day of surgery, she was premedicated with lorazepam plus morphine (more than 1 hour before arriving in the operating room). Anesthesia was induced intravenously with etomidate, fentanyl, and rocuronium, and the electrocardiogram and invasive blood pressure were monitored continuously. After tracheal intubation, a central venous catheter was placed, and cefazolin (2 g diluted in 5% dextrose) was slowly infused. Anesthesia was maintained with sevoflurane and fentanyl. A transesophageal echocardiographic (TEE) probe was introduced, and the TEE examination started.

The patient remained stable until intravenous administration of a 1-mL test dose of aprotinin (10,000 KIU), approximately 40 minutes after anesthetic induction. A sudden increase in ventilatory pressure was noted 3 minutes later. Manual ventilation was attempted but was found to be impossible. Oxygen saturation was 97%, but the end-tidal CO_2 abruptly decreased to 0 (Fig 1). To exclude tracheal tube dislodgment or obstruction, laryngoscopy was performed, the TEE probe was removed, and the endotracheal tube was changed. No extrinsic compression or internal obstruction of the endotracheal tube was found. The clinical situation rapidly deteriorated, with severe shock, bradycardia, and cardiac arrest. Diagnosis of a possible anaphylactic reaction to aprotinin was made.

External cardiac massage was initiated with concomitant administration of intravenous epinephrine boluses, hydrocortisone, inhaled β_2-adrenergic agonists (salbutamol), and intravascular fluid expansion with crystalloid. As soon as possible, infusions of norepinephrine, aminophylline, and sodium bicarbonate were also started. Seven minutes after the beginning of the severe bronchospasm, ventilation improved significantly with the reappearance of measured CO_2 in the capnograph curve. Four minutes later, an acceptable BP was achieved.

Blood samples were taken approximately 60 minutes after the start of the reaction and sent for complement and tryptase measurements. The surgery continued uneventfully. The patient was weaned from cardiopulmonary bypass using inotropic support and transferred to the intensive care unit.

Results of the tryptase and complement measurements, asked for intraoperatively, revealed a tryptase level (measured by fluorescence immunoassay method, UniCAP; Pharmacia & Upjohn, Uppsala, Sweden) of 61.4 μg/L (normal baseline $<$11.5 μg/L), and complement fragments of C3, C4, and CH50 markedly diminished. The patient remained in the ICU for 3 days and was discharged on postoperative day 6, without any evidence of neurologic sequelae.

Some weeks later, immunologic investigations were performed to identify the agent responsible for the anaphylactic reaction. These investigations included skin tests (prick and intradermal tests) and in vitro tests (concentration of specific antilatex immunoglobulin [Ig] E and Basotest; Becton Dickinson, Oxford, UK). A prick test was considered positive when the diameter of the wheal was at least half that produced by codeine. Intradermal tests were considered positive when the diameter of the wheal was at least twice the wheal-injection diameter. In the Basotest, basophil degranulation after drug-induced activation is assessed by the expression of CD63 on the plasma membrane. CD63 is anchored in the basophilic granule membrane, and its exposure to the outside of the cells shows cell degranulation.[2]

Skin tests were negative for fentanyl, etomidate, and latex. Antilatex IgE determination was also negative. The Basotest was positive for aprotinin and also for 3 NMBDs: rocuronium, pancuronium, and atracurium. The Basotest was negative for vecuronium, but the skin tests were positive for this NMBD (Table 1). Moreover, the intradermal test provoked a systemic reaction with flushing, hypotension, and tachycardia.

DISCUSSION

The incidence of anaphylaxis during anesthesia ranges from 1 in 10,000 to 1 in 20,000 anesthetics. Although rare, these reactions may lead to death, even when appropriately treated, with a mortality rate up to 10%.[3] Any substance that patients are exposed to in the perioperative period can produce life-threatening anaphylaxis. The agents most often reported are muscle relaxants (50%-70% of the reactions), latex, antibiotics, colloids, and polypeptides (protamine or aprotinin).[4]

In immunologic terms, anaphylaxis is an example of an immediate type I hypersensitivity reaction. The typical sequence of events begins with the production of IgE in response to initial exposure to an antigen. These antibodies bind to receptors on the surface of mast cells and basophils. When a new contact with antigen occurs, these IgE molecules are bridged by the reintroduced antigen and mast-cell degranulation occurs, releasing potent mediators such as histamine and tryptase.[4] These substances are responsible for the clinical

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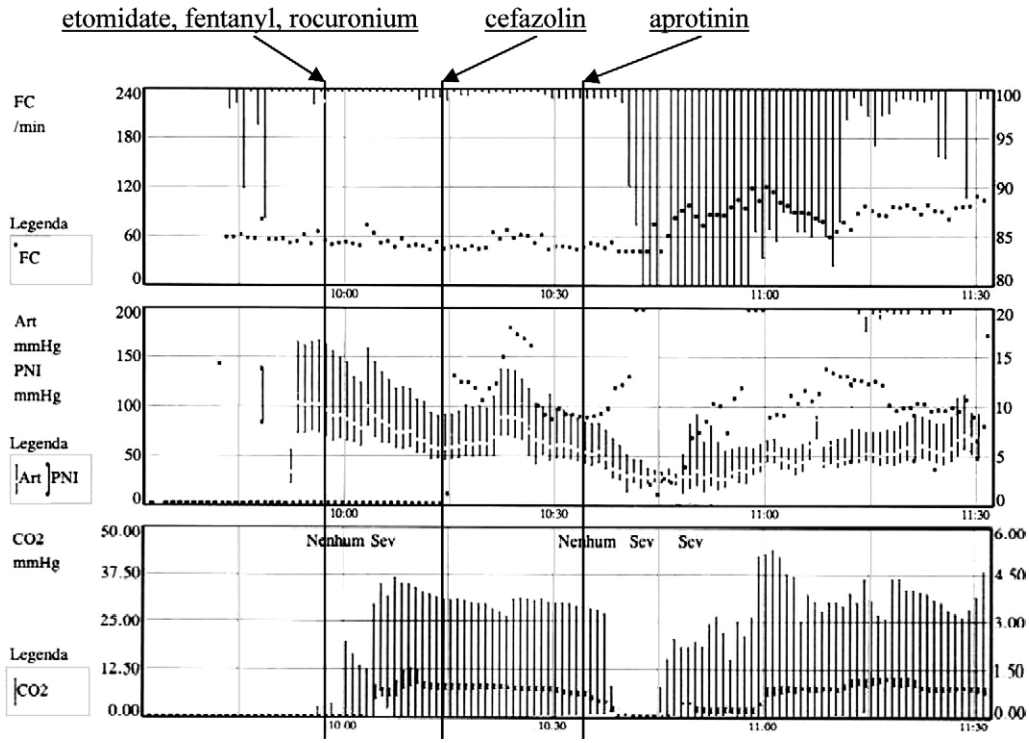

Fig 1. Automated anesthesia record: the upper box contains heart rate (dots) in beats/min (scale on the left) and SpO_2 (vertical bars) in percentage (scale on the right), the middle box contains invasive arterial pressure (vertical bars) and central venous pressure (dots) reported in mmHg (scale respectively on the left and on the right), and the lower box contains expired CO_2 (vertical bars) in mmHg (scale on the left) and expired sevoflurane (small vertical bars) in percentage (scale on the right). Numbers at the bottom of each box represent time of day.

manifestations of immediate hypersensitivity, such as hypotension, bronchospasm, angioedema, or rash.

In this case, the abrupt onset of severe bronchospasm followed by cardiovascular collapse after intravenous administration of the aprotinin test dose raised the clinical suspicion of an anaphylactic reaction to aprotinin. The increased level of serum tryptase (61.4 μg/L) was also consistent with the clinical diagnosis of anaphylaxis (a tryptase level $>$25 μg/L has a predictive value for the diagnosis of anaphylaxis of 92%[5]). Measurement of this biochemical marker of anaphylaxis is important because although suggestive, those symptoms could be produced by mechanisms other than true anaphylaxis (for instance, the direct, nonimmune, histamine release in anaphylactoid reactions).

The identification of the agent(s) responsible for an anaphylactic reaction rely on accurate and detailed clinical history, combined with specialized investigations, including skin tests and laboratory results. In this patient, the chronology of the events strongly points to aprotinin as the offending drug because clinical manifestations appeared 3 minutes after aprotinin administration. Antigenic challenge in a sensitized individual usually produces an immediate reaction, and, although the onset may be delayed up to 20 minutes, 90% of the reactions appear within 5 minutes.[4,6]

Confirmation of the clinically suspected allergy to aprotinin was given by a positive Basotest. This test is highly specific, although it may offer poor sensitivity.[2] Skin tests with aprotinin were not performed because the data from the in vitro test were considered sufficient to identify the offending drug. Moreover, the potential risk of skin testing was feared in this patient with a previous suspected life-threatening anaphylactic reaction triggered only by a test dose. Aprotinin-specific IgE concentration (another in vitro test) has poor sensitivity,[7] a high cost, and was not available for this patient.

Table 1. Allergy Workup

	Skin Test	In Vitro Test
Latex	Prick test negative	Antilatex, IgE negative ($<$0.35 KUA/L)
Fentanyl	Prick test negative	
Etomidate	Prick test negative	
Aprotinin		Basotest positive (1:200 dilution)
Rocuronium		Basotest positive (10^{-2} dilution)
Pancuronium		Basotest positive (10^{-2} dilution)
Atracurium		Basotest positive (10^{-2} dilution)
Vecuronium	Prick test positive	Basotest negative (10^{-2} dilution)
	Intradermal test positive (10^{-3} dilution)	

Aprotinin, a protein isolated from bovine lungs, has had widespread application because of its ability to reduce bleeding. Since its clinical introduction, the anaphylactic potential of aprotinin has been a major concern. Many of the reported aprotinin-induced hypersensitivity reactions were life threatening, and 9% were fatal.[8] Documented risk factors are intolerance to beef, egg white, and milk or previous aprotinin administration. Although the reported incidence of allergic reactions at the first exposure is 0.7%,[9] at re-exposure it goes up to 17%.[10] The exposure–re-exposure interval appears to be critical for predisposing to an allergic reaction; in 70% of the re-exposure reactions, the previous contact occurred less than 3 months before.[8] The levels of aprotinin-specific antibodies begin to decrease a few weeks after exposure and are usually undetectable after 1 year,[8] strongly suggesting that sensitization gradually vanishes over time.

With the wide use of aprotinin, there is a good chance that some patients will have re-exposure to the drug. When aprotinin has been used in a previous operation, the question arises whether the agent should be used during a subsequent surgery. Its administration must be considered on an individual basis. In this case of cardiac reoperation, with a high risk of bleeding, the re-exposure to aprotinin was believed to be justified because the benefits of aprotinin treatment outweighed the relative risk of a rare, albeit serious, allergic reaction. Moreover, the 11-month interval between the 2 exposures did not place this patient at the highest risk of anaphylaxis. At the time this case occurred, the prescribing information for aprotinin stated that the incidence of anaphylactic reaction after re-exposure was increased when re-exposure occurred within 6 months and mentioned hypersensitivity to aprotinin as the only contraindication. However, in December 2006, soon after the occurrence of this anaphylactic reaction, the manufacturer of aprotinin updated the drug labeling to include stronger warnings about the risk of anaphylactic reactions, stating that the use of aprotinin was contraindicated in patients with a known or suspected former aprotinin exposure in the previous 12 months.

As far as the author knows, this is the first report of anaphylaxis after administration of a 1-mL test dose, as recommended by the manufacturer, to an adult patient almost 1 year after the first exposure. There have been previous reports of test-dose anaphylaxis in different situations including when using a 1-mL test dose in pediatric patients (for whom safety of the drug is yet to be established),[10-13] when using 2- to 4-mL test doses,[7,14,15] or when using a 1-mL test dose in adults but with re-exposure intervals of less than 2 months.[12,16,17]

Screening for anaphylaxis with the recommended test dose does not seem to be a safe practice because a severe reaction can be triggered. Screening tests for aprotinin-specific antibodies have been suggested before re-exposure to aprotinin to identify patients at risk of developing an anaphylactic reaction.[8] The absence of aprotinin-specific IgG indicates a low risk of a hypersensitivity reaction because of its excellent negative predictive value of 100% (no anaphylactic reactions in IgG-negative patients, although only 60% of the positive patients would develop anaphylaxis). Thus, patients should only be re-exposed to aprotinin in case of unequivocal expected benefit from its use and, if possible, only after testing for IgG antibodies.[8] For those selected to be re-exposed, recommended preventive measures include pretreatment with an antihistamine (anti-H1 and/or anti-H2) and corticosteroids, although of unproven efficacy, and administration of the test dose only after sternotomy, shortly before the institution of cardiopulmonary bypass.

The diagnostic procedure of anaphylaxis demands investigation of all the drugs administered before the incident. Therefore, tests were also performed for latex, etomidate, fentanyl, and rocuronium. Rocuronium was the relaxant used, but, because of the known cross-reactivity between NMBDs,[3] other commonly used relaxants (pancuronium, atracurium, and vecuronium) were also investigated. Unexpectedly, Basotest gave positive results for rocuronium, pancuronium and atracurium and negative results for vecuronium. Because the Basotest has a good specificity (93%) in the diagnosis of muscle relaxant allergy but a low sensitivity (64%),[4] allowing many false-negatives, and because the highest rate of cross-reactivity is observed with rocuronium and vecuronium (88%),[18] skin tests were done for vecuronium. (The sensitivity of skin tests for muscle relaxants is approximately 95%.[4]) The positive prick and intradermal tests for vecuronium in addition to the results of the Basotest revealed sensitization to the 4 NMBDs. Therefore, this patient is likely to have antibodies that react with the quaternary ammonium group present in all these relaxants.

It could be argued that, because of environmental exposure to quaternary ammonium groups present in cosmetics and cleaning products, specific IgE against these groups are present in 9% of the population,[4] thereby compromising the diagnostic value of the skin tests and Basotest with muscle relaxants. However, in this patient, the intradermal test done with a relaxant (vecuronium) not only was positive but also triggered systemic symptoms, an event that strongly suggests allergy. Given these results, the 4 NMBDs investigated became contraindicated for this patient, and no other NMBD should be administered in the absence of prior testing. Probably, the safest approach is to avoid this group of drugs in the future.

In this patient, the temporal relationship between the administration of rocuronium and the episode did not favor this drug as the likely allergen because almost 45 minutes elapsed between its administration and the episode. However, an earlier mild reaction to rocuronium might have been overlooked. It can also be speculated about a possible role of rocuronium sensitization on the worsening of the reaction to aprotinin.

It is not widely recognized that patients with perioperative anaphylaxis might present more than 1 allergy (double or multiple sensitization). In the 2-year surveys of anaphylaxis during anesthesia by Mertes et al[18,19] and Laxenaire and Mertes,[20] nearly 2% of the patients were found to be sensitized to 2 different agents. A Danish survey also showed that in 7% of perioperative allergic reactions more than 1 allergen was implicated.[21]

The 2 agents involved in this case, aprotinin and rocuronium, are potent allergens. Muscle relaxants are the most frequently involved agents in perioperative anaphylaxis, and among these succinylcholine and rocuronium are the main culprits. Rocuronium is reported in 26% of the anaphylactic reactions caused by NMBDs in France, albeit the relatively low use of this relaxant in the same period (in only 6.5% of patients submitted to anesthetics comprising relaxant administration).[20] Aprotinin also has high allergenic potential but is not a common cause of anaphylaxis simply because it is rarely administered. However,

the incidence of anaphylaxis caused by aprotinin is higher than the incidence caused by rocuronium, even if the highest reported incidence to rocuronium (3 in 10,000 in Norway)[22] is compared with the lowest incidence of anaphylaxis to aprotinin on first exposure (7 in 1,000).[9]

Cefazolin was not investigated. This antibiotic was continued throughout the surgery and in the postoperative period; thus, it is unlikely to have been the cause of the anaphylactic episode. Furthermore, the same antibiotic had already been used in multiple administrations in the prior surgery without any adverse effects.

In summary, this case shows that perioperative anaphylaxis might be caused by more than 1 causative agent. Every patient who experiences a suspected anaphylactic reaction should be thoroughly investigated. Immediate and delayed investigations must be performed to confirm an eventual IgE-mediated allergic reaction, to identify the responsible drugs, and to detect possible cross-reactivity in cases of anaphylaxis to a NMBD. In this case, the allergic workup revealed that the patient was sensitized by 2 different drugs: aprotinin, as expected, and, unexpectedly, rocuronium. This corroborates other authors' conclusions that an informed guess is not a reliable way of determining the cause of a supposed allergic reaction during anesthesia.[21] The identification of the cause of anaphylaxis is not always straightforward, and the lack of a proper diagnosis and appropriate allergy assessment can lead to fatal re-exposure.

This case also shows that re-exposure to just the test dose of aprotinin may be associated with severe reactions, even when the test dose strictly fulfills the manufacturer's recommendations and when the re-exposure interval is almost 1 year. It also highlights the importance of the manufacturer's recent revised warning about the risk of anaphylactic reactions. Screening tests for aprotinin-specific antibodies are strongly advised before any re-exposure. The use of aprotinin must be restricted to selected patients. This redo case, after the patient's first exposure to aprotinin during mitral valve repair, shows the risk associated with its indiscriminate use particularly in patients prone to redo surgery.

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