

Severe Anaphylactic Reaction to Cisatracurium

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Since cisatracurium was introduced in 1995, there has been only one previous report of a minor anaphylactic reaction to this drug (1). We report a severe anaphylactic reaction to cisatracurium in a patient undergoing a diagnostic laparoscopy.

Case Report

A fit, 29-yr-old female patient (56 kg, ASA physical status I) was admitted for a diagnostic laparoscopy. She had no medical history of note, had no history of atopy or allergic reactions to drugs, and had never received a previous anesthetic. There was no family history of atopy. She was receiving no medication on admission.

Diclofenac sodium 100 mg was given rectally 30 min before anesthesia. Full monitoring was established. She then received propofol 200 mg, lidocaine 20 mg, fentanyl 100 µg, midazolam 2 mg, and cisatracurium 10 mg IV. Her trachea was intubated and ventilated with a mixture of oxygen and nitrous oxide with isoflurane. At this stage, the electrocardiogram showed a sinus tachycardia of 145 bpm, and the pulse oximeter reading decreased from 96% to 67%. She was tracheally extubated and reintubated with the same tracheal tube, but there was no improvement in oxygen saturation. On auscultation, there was good air entry in both lungs with no signs of bronchospasm, and airway pressures did not exceed 30 cm H₂O on manual ventilation. However, heart sounds were faint, and no carotid pulse was palpable. The patient appeared pale, and the capillary filling time was poor. The pulse oximeter and the noninvasive blood pressure monitoring were unrecordable.

A diagnosis of anaphylactic shock was made. Cardiopulmonary resuscitation was started, and epinephrine 0.5 mg was given IV. Two 14-gauge cannulae and a central venous cannula were inserted. She received 3 L of crystalloid and 1 L of colloid. Another dose of epinephrine 0.5 mg was given IV. After approximately 20 min, a satisfactory carotid pulse was palpable, and the noninvasive blood pressure monitoring showed a blood pressure of 122/60 mm Hg. Hydrocortisone 200 mg IV was then given.

One hour after the event, the patient was hemodynamically stable and began making good inspiratory efforts. The neuromuscular blockade was reversed with neostigmine

2.5 mg and glycopyrrolate 0.5 mg. The surgery was canceled, and the patient made a full recovery with no neurological sequelae. EDTA blood samples were taken 0, 4, 9, and 24 h postreaction for plasma tryptase, and urine samples were taken at 4 and 24 h for methylhistamine. This showed very high levels of plasma tryptase and urinary methylhistamine (Tables 1 and 2).

Epidermal skin prick testing was performed 4 wk later. A positive result was seen with cisatracurium at a 1:100 dilution. All of the other drugs tested gave negative responses down to a 1:10 dilution, with the exception of morphine, which gave a weak positive response at this dilution (Table 3).

The patient was fully informed of the test results, and arrangements were made for her to receive a Medicalert bracelet. She returned 6 wk later for a laparoscopy under general anesthesia. Etomidate, fentanyl, and vecuronium were used, and the operation was uneventful.

Discussion

There are 5,000–10,000 documented cases of drug-induced severe anaphylactic reactions in the United Kingdom every year (2). The risk of developing a severe anaphylactic reaction during anesthesia has been estimated at 1:4,600 procedures, with a mortality rate of 6%. Neuromuscular blocking drugs are the leading cause of perioperative anaphylaxis (3), with 48% of cases caused by suxamethonium. Vecuronium and atracurium account for 12% and 18% of cases, respectively (4). Atracurium has a low incidence of anaphylaxis. Cisatracurium, 1 of the 10 isomers of atracurium, would therefore be expected to have a similar profile, as we can find no evidence to suggest that stereoisomers of the same drug produce different immune responses.

It is clinically impossible to distinguish an anaphylactic reaction from that of an anaphylactoid reaction. The only difference is in the mechanism of histamine release. In anaphylactic reactions, this is caused by the cross-linkage of antigen to immunoglobulin E (IgE) on the mast cell surface (5). In contrast, anaphylactoid reactions are a result of direct release or complement activation (6). In the case of cisatracurium, this is compounded by the absence of a test for specific IgE.

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Table 1. Serum Tryptase Versus Time

Time (h)	Tryptase levels ($\mu\text{g/L}$)
0	57.1
4	45.1
9	23.4
24	13.0

Table 2. Urinary Methylhistamine Versus Time

Time (h)	Methylhistamine ($\text{ng}/\mu\text{mol}$)
4	193.5
24	24.7

Table 3. Skin Prick Tests

Test drug	Dilution		
	1:1000	1:100	1:10
Negative control (saline)	—	—	—
Positive control (0.1% histamine)	++	++	++
Cisatracurium	—	++	NT
Etomidate	—	—	—
Fentanyl	—	—	—
Lignocaine	—	—	—
Midazolam	—	—	—
Morphine ^a	—	—	—
Propofol	—	—	—
Voltarol	—	—	—

NT = not tested.

^a Stock concentration 10 mg/mL; therefore, 1:1000 dilution = 10 $\mu\text{g/mL}$, 1:100 dilution = 100 $\mu\text{g/mL}$, and 1:10 dilution = 1 mg/mL.

However, this patient's reaction was likely anaphylaxis because a positive skin prick test at a 1:100 dilution is highly indicative of the presence of specific IgE to cisatracurium (7).

Prior exposure is not always necessary: 30% of individuals with severe anaphylactic reactions to neuromuscular blockers have had no previous exposure to the drug (2). Previous exposure may be the result of cross-reactivity to the quaternary ammonium ion found in other products, such as drugs, foods, and cosmetics (8). The high incidence of anaphylactic reactions to neuromuscular blockers in women may be explained by their increased exposure to cosmetics and cleaning products. Our patient was given vecuronium for her second operation. It is known that there is some cross-reactivity among the nondepolarizing muscle relaxants (9); ideally, vecuronium and other muscle relaxants should have been included in the panel of drugs that was used for skin prick testing.

An increasingly recognized cause of perioperative anaphylaxis is latex allergy (10). However, our patient had no history of allergic symptoms on exposure to latex, and her specific IgE test to latex was negative, which makes latex-induced anaphylaxis unlikely.

A further point of interest with this case was that cardiovascular collapse was the only presenting sign. Although cardiovascular signs develop in 90% of anaphylactic reactions, other features, such as bronchospasm, urticaria and angioedema, and abdominal pain often occur. The incidence of cardiovascular collapse occurring in isolation is only 10%. Watkins (4) found that atracurium was more likely to result in hypotension, whereas vecuronium caused bronchospasm. Previous adverse reactions for cisatracurium reported to the Committee on the Safety of Medicines have documented one case each of hypotension, bradycardia, supraventricular tachycardia, bronchospasm, and urticaria. However, none of these cases was supported by any laboratory or immunological testing, and the mechanisms remain unknown.

Anaphylactic reactions are rare. It is vital that all anesthetists be familiar with the "anaphylaxis drill" because even the most severe reactions promptly and successfully respond to appropriate treatment. The Association of Anaesthetists of Great Britain and Ireland (1995) (11) recommends the following guidelines for the initial management of a patient with suspected anaphylaxis during anesthesia:

- Stopping administration of the drug(s) likely to have caused the anaphylaxis
- Maintain airway and administer 100% oxygen. Check for breath sounds and peripheral pulses. If these are absent, cardiopulmonary resuscitation must be instituted.
- Give epinephrine 50–100 μg IV over 1 min (0.5–1 mL of 1:10,000) for hypotension with titration of further doses as required. In a patient with cardiovascular collapse, 0.5–1 mg (5–10 mL of 1:10,000) may be required in divided doses by titration.
- Start intravascular volume expansion with crystalloid or colloid.
- Consider secondary therapy such as epinephrine infusions, antihistamines, corticosteroids, bronchodilators, and bicarbonate.

The diagnosis of anaphylaxis is based on clinical grounds. Biochemical tests, such as serum tryptase and urinary methylhistamine, are useful in confirming the occurrence of anaphylaxis. Identification of the drug requires immunological tests; for example, drug-specific antibodies and skin prick testing.

Tryptase is stored in mast cell granules and is released with histamine during the degranulation process. Unlike histamine, which remains in plasma for a short time (15–60 min), tryptase levels are increased for a longer period (3 h) (12). Another marker is urinary methylhistamine, a metabolite of histamine that has a longer half-life than histamine (2–3 h). With these markers, a retrospective diagnosis can be made after the initial treatment of the patient.

Skin prick testing is the method used to confirm specific drug sensitivity. The test is performed by the introduction of the suspected allergen to the skin. A reaction is characterized by the appearance of a wheal, which is highly predictive of sensitization (13). A positive reaction can be the result of an IgE-mediated reaction or direct histamine release. Certain drugs, such as opioids, have intrinsic histamine-releasing activity, and positive results can be observed at 1:10 dilution. However, positive reactions at a 1:100 dilution are highly suggestive of an IgE-mediated reaction (11).

This is the first reported case of a severe anaphylactic reaction to cisatracurium requiring cardiopulmonary resuscitation. Despite the many benefits of cisatracurium over atracurium, there still remains the potential for severe anaphylaxis.

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