

CASE REPORTS

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Anaphylactic Reaction after Cisatracurium

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Many well-described adverse drug effects, including anaphylactic and anaphylactoid reactions, have occurred after administration of neuromuscular blocking agents.^{1,2} Several reports of anaphylactic reactions after administration of atracurium have appeared.^{3,4} Cisatracurium is a new nondepolarizing muscle relaxant that chemically is an isomer of atracurium. We report on an anaphylactic reaction to cisatracurium with a patient's first exposure to a muscle relaxant.

Case Report

A 70-yr-old woman (weight, 50 kg; height, 153 cm), American Society of Anesthesiologists' physical status II, was scheduled for left carotid endarterectomy. Her medical history was significant for diet-controlled diabetes mellitus. Previous operations, in the 1960s, were a breast biopsy and a dilation and curettage during general anesthesia without the administration of a neuromuscular blocking agent. Daily medication was 81 mg of aspirin. The patient was allergic to trimethoprim-sulfamethoxazole (Bactrim) and trimethoprim (Trimprax).

Preoperative medications given intravenously 30 min before induction were midazolam, 2 mg, and cefazolin, 1 g. In the operating room, standard monitors were applied, including electrocardiogram (leads II, V) and electroencephalogram. The patient's blood pressure was 124/68 mmHg, with a sinus rhythm of 88 beats/min. General anesthesia was induced with propofol, 120 mg, succinylcholine, 100 mg, and fentanyl, 100 µg, intravenously without significant change in heart rate or blood pressure. After tracheal intubation, anesthesia was maintained with isoflurane, 0.4%, and nitrous oxide, 60%, with oxygen. A catheter was placed in the right radial artery. Monitoring of neuromuscular blockade at the ulnar nerve indicated return of neuromuscular function.

Ten minutes after induction, 8 mg (0.16 mg/kg) of cisatracurium was given in a rapidly infused intravenous dose. During this time, the patient was being prepared for surgery, and her blood pressure was 118/64 mmHg, with a heart rate of 84 beats/min. Approximately 90-120 s after administration of cisatracurium, the patient had acute onset of sinus bradycardia (heart rate, 85 to 50 beats/min) followed by a decrease in blood pressure to 85/40 mmHg. Administration of isoflurane and nitrous oxide was discontinued, and preparation of the neck was stopped. The bradycardia lasted 30 s. Blood pressure decreased to 40 mmHg systolic, and the cardiac rhythm changed to sinus tachycardia with a rate of 110 beats/min.

A 500-ml fluid bolus of lactated Ringer's solution was administered intravenously. A phenylephrine infusion begun at 150 µg/min was followed by an increase in blood pressure to 60/34 mmHg. The skin in the truncal area was flushed without urticaria. The SaO₂ value decreased from 100% to 93%. Breath sounds were decreased bilaterally without audible wheezing; the peak inspiratory pressure increased from 15 to 35 cmH₂O. The electrocardiograph showed ST-T wave depression in leads II and V. Blood pressure increased to 90/58 mmHg after administration of 100 µg of epinephrine, which was repeated, and an epinephrine infusion at 4 µg/min was started. The duration of hypotension was 12 min, and the electroencephalographic tracing remained unchanged. Blood pressure slowly increased to 122/70 mmHg, the ST-T wave depression resolved, and the electrocardiographic tracing returned to baseline. The SaO₂ value increased to 100%, and the peak inspiratory pressure decreased from 35 to 20 cmH₂O. Methylprednisolone, 125 mg, and diphenhydramine, 25 mg, were administered intravenously. Because of the hemodynamic instability, the procedure was canceled.

The patient was transported to the postanesthesia care unit 60 min after the onset of the adverse reaction. Her trachea remained intubated, and her lungs were mechanically ventilated. Her blood pressure was 148/64 mmHg, with a sinus rhythm of 80 beats/min. The patient was given an additional 25 mg of diphenhydramine and 20 mg of famotidine. The epinephrine infusion was slowly discontinued. Train-of-four stimulation of the ulnar nerve 70 min after administration of cisatracurium showed four visible responses of the adductor pollicis muscle. The patient was given neostigmine, 3.5 mg, and glycopyrrolate, 0.4 mg. She was awake, and her trachea was extubated without incident. The patient had no recall of the event and an uneventful recovery.

Blood obtained in the postanesthesia care unit showed an increased tryptase concentration of 14 U/l (expected value, < 0.5 U/l). Tryptase is a major constituent of the secretory granules of human mast cells and is released along with histamine from an immunologically activated mast cell. The serum level of prostaglandin D₂ was 114 pg/ml (expected value, 35 to 115 pg/ml; release is in the early phase of anaphylactic reactions). Allergy testing for cisatracurium was performed by the skin prick technique. A small amount of erythema

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appeared at a concentration of 1:100 and a wheal and flare at 1:10. Full concentration of cisatracurium produced a significant wheal and flare. Skin testing by prick and intradermal injection to rocuronium, succinylcholine, and propofol yielded negative results. Skin test results with the same concentration of cisatracurium in two healthy control subjects were negative.

Two weeks after her previous anesthesia, the patient was pre-treated with H_1 and H_2 receptor blockers and received an uneventful anesthesia with propofol, rocuronium, and fentanyl.

Discussion

Anaphylaxis is an acute, severe, and potentially life-threatening reaction that often is difficult to recognize during general anesthesia. The incidence of anaphylactic reactions during general anesthesia has been estimated to be 1 in 6,000, with neuromuscular blocking agents responsible for 80% of the cases.⁵

The diagnosis of anaphylactic reaction usually is based on clinical suspicion. Biochemical studies may be helpful in confirming the diagnosis. Our patient had an increased serum tryptase level. Tryptase is a neutral protease stored in mast cell granules, which are released along with histamine during mast cell degranulation. Unlike histamine, which increases early and decreases rapidly in the blood during anaphylaxis (peaks at about 5 min and returns to baseline within 15–60 min), tryptase increases later and remains elevated for a longer period (peaks at 1–2 h and remains high for several hours).⁶

Another marker of mast cell degranulation is prostaglandin D_2 . Mast cells stimulated by anti-immunoglobulin E (IgE) release prostaglandin D_2 and histamine, whereas nonimmunologically activated cells release histamine but not prostaglandin D_2 .⁷ Our patient's concentration of prostaglandin D_2 was at the upper limit of normal, indicating an IgE-mediated reaction. Laroche *et al.*⁶ recommended that if anaphylaxis is suspected, a plasma histamine sample should be drawn immediately after the reaction, and another sample should be collected 1–2 h later (no longer than 6 h) to measure serum tryptase.

Patients who have experienced anaphylactic reactions in the operating room require evaluation to identify the causal agent and to guide selection of medication for future anesthesia. Identification of the drug may be difficult because many medications are administered in a relatively short time. Skin testing is the method generally used to confirm specific drug sensitivity in patients after an anaphylactic reaction. Skin tests are standardized for IgE-mediated reactions and are highly

specific.⁸ After intradermal injection of the suspected allergen, an immediate reaction is characterized by the appearance of a wheal and flare, which is highly predictive of sensitization. Leynadier *et al.*⁹ found a significant correlation between prick tests and intradermal injection in identifying the causative agent.

Cross-reactivity of neuromuscular blocking agents is frequent because of the quaternary ammonium radicals associated with this class of drugs. Cross-reactivity depends on the configuration of the antibody that is related to the structure of the molecule (distance between the quaternary ammonium ions, flexibility of the molecule). Muscle relaxants with a rigid backbone between the ammonium ions (pancuronium) are less reactive than those with flexible molecules (succinylcholine).¹⁰ It is essential that any patient with a history of an allergic reaction to a neuromuscular blocking agent be tested for cross-reactivity. Laxenaire *et al.*¹¹ demonstrated that when other neuromuscular blocking agents are evaluated, intradermal skin testing is needed because of false-negative results associated with prick tests. Our patient had a positive skin prick test result to cisatracurium but negative results to skin prick and intradermal testing with rocuronium and succinylcholine.

Cisatracurium, chemically an isomer of atracurium, is a benzyliisoquinolinium-type muscle relaxant with an intermediate duration of action. Early clinical reports have shown that cisatracurium does not cause histamine release or clinically significant cardiovascular effects at doses of eight times its ED_{95} (0.4 mg/kg).¹² In our patient, cutaneous signs of truncal flushing and erythema developed 4 min after administration of cisatracurium and spread over the entire body, a reaction clinically similar to that described as caused by histamine release after administration of atracurium.^{13,14} Flushing and significant cardiovascular effects after administration of cisatracurium are highly suggestive of histamine release caused by an allergic type of reaction.

As in our patient, many patients with anaphylactic reactions have had no previous exposure to neuromuscular blocking drugs. An IgE-mediated reaction may occur on the first administration of these agents if the patient has been exposed to one of their components. The mechanism of anaphylactic reaction to muscle relaxants was suggested by the finding of cross-reactivity between muscle relaxants and substances with quaternary ammonium ions.¹⁵ Sensitization to neuromuscular blocking agents is caused by the quaternary ammonium components of these drugs, which also are widely found in other drugs, foods, soaps, and cosmetics.¹⁶ The

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high incidence of anaphylactic reaction to neuromuscular blocking agents in women may be explained by increased exposure to cosmetics and cleaning agents.¹⁷

Through an increased serum tryptase level and positive skin test results, we demonstrated an IgE-mediated anaphylactic reaction to cisatracurium in a patient's first exposure to a neuromuscular blocking agent. Anaphylactic reactions may be challenging to recognize during general anesthesia. Cisatracurium has been shown in previous studies not to cause histamine release or clinically significant cardiovascular effects. Two of the early signs of anaphylaxis in our patient were hypotension and cutaneous flushing, not expected effects of cisatracurium.

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