Rocuronium anaphylaxis and multiple neuromuscular blocking drug sensitivities

Peter Matthey MB FFARCSI,*
Pei Wang MB FFARCSI,†
Barry A Finegan MB FRCPC,*
Maria Donnelly MB FFARCSI†

Purpose: To report a case of anaphylaxis to rocuronium and the sensitivities to multiple neuromuscular blocking drugs in a patient with no previous exposure to this group of drugs. We describe the current recommendations for both intraoperative and postoperative testing of these patients.

Clinical Features: A 36-yr-old man was admitted for repair of a ruptured Achilles tendon. Following induction of general anesthesia with fentanyl and propofol, 60 mg of rocuronium were given to facilitate tracheal intubation. He immediately became profoundly hypotensive with impalpable pulses, and blood pressure could not be recorded. Airway pressure increased markedly, and hand ventilation of the lungs became very difficult. His airway was secured and he was successfully resuscitated with 3 mg epinephrine and three litres crystalloid and colloid intravenous fluid therapy. His recovery in the intensive care unit was uneventful and the operation was performed four days later under spinal anesthesia. Subsequent skin prick testing, performed six weeks later, demonstrated strong positive weal and flare reactions to rocuronium, vecuronium and pancuronium, and some cross-reactivity with the benzylisoquinolinium group of muscle relaxants.

Conclusion: Muscle relaxants are responsible for 61.6% of cases of anaphylaxis during general anesthesia. Cross-reactivity is common, as this group of drugs share a quaternary ammonium group. It is mandatory that patients be tested for both the agent responsible and cross-reactivity following an anaphylactic response. We suggest a protocol for investigation of suspected anaphylaxis.

Objectif : Rendre compte d'un cas d'anaphylaxie au rocuronium et de sensibilité à de multiples myorelaxants chez un patient non exposé auparavant à ce genre de médicaments. Décrire les recommandations courantes de tests peropératoires et postopératoires à réaliser dans de tels cas.

Éléments cliniques : Un homme de 36 ans a été admis pour la réparation d'une rupture de tendon d'Achille. Après l'induction de l'anesthésie générale avec du fentanyl et du propofol, on a administré 60 mg de rocuronium pour faciliter l'intubation endotrachéale. Une importante hypotension s'est immédiatement installée, les pouls étaient impalpables et la pression sanguine ne pouvait être enregistrée. La pression a beaucoup augmenté dans les voies aériennes et la ventilation manuelle des poumons est devenue très difficile. On a libéré les voies aériennes et le patient a été réanimé avec succès suivant l'administration intraveineuse de 3 mg d'épinéphrine et de 3 L de cristalloïde et de colloïde. La récupération s'est déroulée sans incident à l'unité des soins intensifs et l'opération a été réalisée quatre jours plus tard sous rachianesthésie. Le test de cutiréaction pratiqué ultérieurement, six semaines après l'opération, a montré une réaction papulo-érythémateuse fortement positive au rocuronium, au vécuronium et au pancuronium ainsi qu'une réaction croisée avec les myorelaxants du groupe benzylisoquinolinium.

Conclusion : Les myorelaxants sont responsables de 61,6 % des cas d'anaphylaxie pendant l'anesthésie générale. La réaction croisée est courante, car ce type de médicaments partage un groupe d'ammonium quaternaire commun. Il faut absolument que les patients subissent des tests pour vérifier la réaction croisée et la sensibilité à l'agent responsable d'anaphylaxie. Nous recommandons un protocole d'examen dans les cas d'anaphylaxie présumée.

From the Department of Anesthesia and Intensive Care, Adelaide and Meath Hospitals,† Incorporating The National Children's Hospital, Dublin, Ireland and Department of Anesthesia, Walter C. Mackenzie Health Sciences Centre,* University of Alberta, Edmonton, Canada.
Address correspondence to: Peter Matthey MB, Department of Anesthesia, 3B2.32 Walter C Mackenzie Health Sciences Centre, University of Alberta, Edmonton, T6G 2B7 Canada. Phone: 780-407-8861; Fax: 780-407-3200; E-mail: pmatthey@ualberta.ca
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ROCURONIUM is an aminosteroid non-depolarising muscle relaxant and shares many pharmacological features with vecuronium. Rocuronium's main benefits are rapid onset of neuromuscular blockade with minimal cardiovascular side-effects and negligible histamine release.[1,2]

We report a patient who developed anaphylactic shock following administration of rocuronium. Subsequent testing revealed sensitivity to many of the non-depolarising muscle relaxants in current use.

Case Report

A 36-yr-old, 80 kg healthy male tourist was scheduled to undergo repair of a ruptured Achilles tendon under general anesthesia. He had undergone previous uneventful dental anesthesia and had no history of allergies or atopy. Patient monitoring included continuous electrocardiography (ECG), non-invasive blood pressure monitoring, pulse oximetry (SpO_2), airway pressure and end-tidal carbon dioxide ($ETCO_2$) measurement.

Anesthesia was induced with 100 μg fentanyl and 150 mg propofol with 20 mg lidocaine. Once the ability to ventilate the lungs had been confirmed, 60mg rocuronium were administered to facilitate tracheal intubation.

Immediately following rocuronium administration the lungs became extremely difficult to ventilate with bag and mask. Emergency intubation was performed and auscultation revealed bronchospasm. Concomitant with this a supraventricular tachycardia of 180 beats·min^{-1} was noted on ECG. Pulses were impalpable and SpO_2 and $ETCO_2$ were unrecordable. Profound bradycardia of 30 beats·min^{-1} followed and cardiopulmonary resuscitation was promptly initiated. Atropine, 0.6 mg, 3 mg epinephrine in divided doses and volume loading with two litres of saline and one litre of gelofusin were given over the next 20 min. At this point, blood pressure returned, but an adrenalin infusion at 7 μg·kg^{-1}·min^{-1} was required to maintain a systolic pressure of greater than 80 mmHg. Hydrocortisone, 200 mg, was also administered.

The procedure was canceled and the patient was transferred to the intensive care unit (ICU). By this time generalized edema, more prominent in the facial area, was noted. The epinephrine infusion was discontinued 60 min after ICU admission. Tracheal extubation was achieved three hours later. Subsequent recovery was uneventful.

Skin prick testing, performed two days later, demonstrated a strong reaction to rocuronium bromide, with negative results for fentanyl, propofol and lidocaine. Serum tryptase levels taken at the time of the event could not be processed due to a storage error. The operation was performed four days after the initial event under spinal anesthesia, using 0.5% bupivacaine, without incident.

The results and implications of this event were explained to the patient and arrangements were made for him to have a further series of skin prick tests on his return home. A Medic-Alert bracelet was supplied.

More extensive skin prick testing was performed in his local hospital six weeks later. This revealed strong positive weal and flare reactions to rocuronium, vecuronium and pancuronium. A 3 mm weal developed in response to cisatracurium, demonstrating cross-reactivity with the benzylisoquinolinium group of muscle relaxants. Tests for succinylcholine were negative.

Discussion

Muscle relaxants are the commonest group of anesthetic drugs implicated in perioperative anaphylaxis. A recent report from the French Perioperative Anaphylactoid Reactions Study Group found that 61.6% of anaphylactic reactions were due to muscle relaxants, with vecuronium, atracurium and succinylcholine responsible for 30.5%, 25.1%, and 24.8% respectively.[3]

Clinically, it is not possible to differentiate anaphylactoid from anaphylactic shock and histamine is involved in both processes, though an IgE mechanism predominates in allergic reactions to non-depolarising muscle relaxants.[4] The main antigenic determinants of non-depolarising muscle relaxants are the tertiary and quaternary ammonium groups, which are common to all of this class of drugs. Consequently the potential for cross reactivity exists, though it is unusual to be allergic to all non-depolarising muscle relaxants.[5,6] To date only three cases of rocuronium anaphylaxis have been reported.[4,7] In one case report a patient suffered an anaphylactic reaction to rocuronium but negative results were obtained in response to testing with vecuronium, pancuronium, pipercuronium, d-tubocurarine and atracurium. The case described in our report is unusual in that sensitivity to many of the non-depolarising muscle relaxants in common use today occurred.

Cross-reactivity of rocuronium has recently been evaluated in a series of thirty-one patients known to have had hypersensitivity reactions to a variety of neuromuscular blocking agents.[8] Ten of these patients exhibited the presence of specific IgE against the quaternary ammonium group on radioimmunoassay (QAS-RIA), but cross-reactivity could not be demonstrated using intradermal and *in vitro* leukocyte histamine release (LHRT) testing for rocuronium. The

LHRT test had demonstrated 83% specificity for evaluating *in vitro* cross-reactivity between steroid muscle relaxant drugs in this series. Laxenaire *et al.* concluded that rocuronium had a low potential for anaphylaxis and suggested that it could be considered as an alternative agent in those known to be allergic to other muscle relaxants, provided that intradermal testing was negative.

The clinical features, response to treatment and subsequent test results suggest that our patient suffered an anaphylactic response to rocuronium. Unfortunately, we were unable to prove this conclusively in the absence of serum tryptase levels. The striking feature of this case was the presence of multiple allergies to muscle relaxants.

As anaphylactic reactions are uncommon, this case also serves to highlight the importance of having a protocol in place to guide the clinician in performing the appropriate laboratory tests at the time of a suspected reaction (Table). These tests will subsequently aid in confirming or refuting a diagnosis of anaphylaxis. As these tests are specialized and reactions may occur outside of normal laboratory working hours, correct storage and processing of samples is vital. Immunological and biochemical proof of anaphylaxis requires elevated levels of histamine and tryptase, together with demonstration of specific IgE. Serum ß-tryptase, plasma histamine and urinary methyl-histamine levels are the most useful immediate tests. Elevated ß-tryptase concentrations demonstrate that mast-cell activation with mediator release has occurred, the level generally reflecting the severity of the reaction. The initial sample must be obtained within one to two hours of the reaction and a further sample is usually obtained five to six hours later. ß-tryptase serum samples remain stable for several days when correctly stored. Plasma histamine concentrations return to baseline within 30 to 60 min of the reaction and must therefore be drawn immediately. Sample processing must not be delayed, as spontaneous basophil histamine release will occur, resulting in falsely elevated histamine levels. Urinary methyl-histamine remains elevated for longer and may thus be more useful.[9]

It is considered mandatory that attempts are made to identify the drug responsible for an anaphylactic reaction, and that any cross-reactivity among muscle relaxants is also identified.

Intradermal testing is the method of choice for this, though skin prick testing has also been shown to have a sensitivity and specificity of over 95% for succinylcholine, pancuronium and vecuronium.[10–12] Intradermal testing is best performed approximately one month after the initial episode.[13]

TABLE Investigation protocol for suspected anaphylaxis

1. Do not attempt any investigations until emergency treatment has been completed.
2. Make a detailed written record of all events, including timing of administration of drugs in relation to the onset of the reaction.
3. Draw blood samples for serum ß-tryptase at 1, 3 and 24 hours after onset of reaction. Use serum collection tube. Separate blood as quickly as possible. Store separated serum at -20°C unless it can be processed immediately.
4. Draw blood sample for plasma histamine. Process immediately.
5. Collect urine for determination of urinary methyl-histamine concentrations. Timed collection. Requires acetic acid bottle.
6. Perform intradermal testing four to six weeks after the event to identify the agent responsible for the reaction. Current recommended dilutions are 10^{-1} to 10^{-4} for intradermal testing, and 10^{-1} for skin prick testing. Ideally these tests should be performed in an allergy clinic by experienced personnel.
7. In the case of muscle relaxants, identify any cross-reactivity.
8. Explain the importance of the reaction to the patient and provide a Medic-Alert bracelet.
9. Report the event to the appropriate regulatory body.

With respect to muscle relaxants, Laxenaire *et al.* suggest performing intradermal tests on the back using 10^{-4} to 10^{-1} dilutions of the commercially available drug preparations. Injections are given every 15-20 min starting with a 10^{-4} dilution when a prick test, using undiluted drug, is positive and starting with a 10^{-3} dilution when the prick test is negative, and ending with the lowest dilution as long as the results seem negative. A positive prick test is deemed to have occurred if the resulting wheal is at least half the diameter of that produced by a control test using 9% codeine phosphate solution. Skin tests are interpreted after 15 min: a positive reaction results in a pale pink wheal and surrounding flare. Intradermal tests are positive when the diameter of the wheal is more than 5 mm with a surrounding flare.[8]

Other tests for cross-reactivity include LHRT and QAS-RIA but, as they do not have a higher sensitivity than intradermal testing and are considerably more difficult to perform, they are more useful in confirming the results of skin tests in dubious cases.

In conclusion, drug related anaphylactic reactions in anesthesia are uncommon, but are most frequently due to the aminosteroid group of non-depolarising muscle relaxants. Cross-sensitivity can occur and must be identified. The patient should be advised with respect to future options once the results of testing are available.

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