

Case Reports

Failure to investigate anaesthetic anaphylaxis resulting in a preventable second anaphylactic reaction

A. F. PEDERSEN*, S. GREEN†, M. A. ROSE‡

Department of Anaesthesia, Royal North Shore Hospital, Sydney, New South Wales, Australia

SUMMARY

We present a case of anaphylaxis to suxamethonium and/or vecuronium in a patient who had previously suffered an anaphylactic reaction, presumably to rocuronium. The patient had not been referred for formal allergy testing after the first anaphylactic reaction. Subsequent formal allergy testing revealed sensitivities to suxamethonium, rocuronium and vecuronium. Her next anaesthetic, using cisatracurium, was uneventful. It is recommended that all patients with suspected perioperative anaphylaxis are referred for testing. This is the responsibility of the anaesthetist. Particular caution should be used with suspected neuromuscular blocking drug allergy as cross-reactivity is common and not predictable by drug structure.

Key Words: anaphylaxis, suxamethonium, rocuronium, rocuronium, allergy testing

We report a case that highlights the importance of appropriate referral of cases of perioperative anaphylaxis to a testing centre for identification of the causative agent. Identification of alternative agents that are not likely to cross-react is equally necessary. It is important to recognise that simply avoiding all drugs that were used during an anaesthetic complicated by anaphylaxis is not necessarily a safe practice, as some classes of drugs (particularly neuromuscular blockers and antibiotics) have frequent and unpredictable cross-reactivity.

CASE HISTORY

Consent to publish this information was obtained from the patient.

A 65-year-old female was scheduled for removal of a gastric band that had been inserted three years earlier, as it was causing her back pain and reflux. She weighed 85 kg and her past medical history included hypertension, mild asthma and type 2 diabetes mellitus. Her medications were gliclazide, candesartan, nifedipine, salbutamol and hormone replacement therapy. Her only quoted drug allergy was to rocuronium.

Prior to 2008 she had undergone several uneventful general anaesthetics, including a cholecystectomy, for

which rocuronium was used without adverse effect. However, when her gastric band was inserted in 2008, she had a significant hypotensive episode (systolic blood pressure 60 to 80 mmHg) and tachycardia. Drugs given prior to the reaction were midazolam, cephalothin, alfentanil, propofol and rocuronium. Treatment included adrenaline boluses and an adrenaline infusion, and she required postoperative intensive care. There is no record of a mast cell tryptase assay being taken. The surgeon organised for her to wear a medic alert bracelet warning of allergy to rocuronium, which was presumed to be the causative agent. The patient was not investigated at this time to confirm the diagnosis, nor to check for cross-reactivity to other neuromuscular blocking agents (NMBA). Induction of general anaesthesia for the removal of her gastric band was with midazolam 1 mg, fentanyl 100 µg, droperidol 750 µg and propofol 100 mg. A remifentanyl infusion was used for maintenance. Suxamethonium 100 mg was used to facilitate tracheal intubation preceded by a priming dose of vecuronium (0.5 mg). After the administration of the vecuronium and suxamethonium, a severe anaphylactic reaction ensued. After intubation, her initial systolic blood pressure measured non-invasively was 60 mmHg. However, soon after, her carotid pulse became impalpable and advanced life support was initiated.

During the resuscitation, she received a total of adrenaline 7 mg, hydrocortisone 250 mg, promethazine 25 mg, 11 litres of crystalloid and 1 litre of colloid. After 30 minutes, a noradrenaline infusion

* BSc, MB, BS, FANZCA, Provisional Fellow.

† MBBCh, FCA(SA), FANZCA, Visiting Medical Officer and Anaesthetist.

‡ MB, BS, BSc (Med), FANZCA, Visiting Medical Officer and Anaesthetist.

Address for correspondence: Dr M. A. Rose. Email: rnsaac@gmail.com

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was commenced and the cardiovascular situation stabilised. She was transferred to the intensive care unit and was successfully extubated the following morning.

Mast cell tryptase assays were taken. The initial level was greater than 200 $\mu\text{g/l}$ and the level at four hours was 157 $\mu\text{g/l}$; both well in excess of the upper limit of normal for the assay (13.5 $\mu\text{g/l}$), thus confirming the diagnosis of anaphylaxis¹.

The patient was subsequently referred for formal allergy testing. She was tested intradermally in the presence of positive and negative controls using standardised dilutions to midazolam, fentanyl, droperidol, vecuronium, propofol, remifentanyl, suxamethonium, rocuronium, pancuronium and cisatracurium. Measurement of specific immunoglobulin E (sIgE, Immunocap®, Phadia, Uppsala, Sweden) was performed to morphine and pholcodine (used to detect immunoglobulin E [IgE] antibodies that would cross react with neuromuscular blockers) and also latex. Positive intradermal responses were seen to vecuronium, suxamethonium and rocuronium. All other substances tested were negative. The sIgEs were positive to morphine and also to pholcodine, which is in keeping with allergy to NMBAs. The sIgE test to latex was negative.

These tests indicate that the cause of the second anaphylactic reaction was likely to have been vecuronium and/or suxamethonium. The evidence suggests that rocuronium caused the anaphylactic reaction in 2008. She was advised to avoid rocuronium, vecuronium and suxamethonium, and to have her Medic Alert bracelet updated to read "anaphylaxis to rocuronium, vecuronium, suxamethonium". Cisatracurium and pancuronium appeared to be safer alternatives for the future. She was also advised that, as with all patients who have had anaphylaxis under anaesthesia, any future elective anaesthesia should occur at a hospital with intensive care services.

Several months after her second anaphylaxis, the patient was anaesthetised uneventfully for removal of her gastric band with cisatracurium used as the NMBA.

DISCUSSION

This case demonstrates that it is an important responsibility of anaesthetists to arrange formal allergy testing and follow-up of patients who have a suspected anaphylactic reaction during anaesthesia. It is likely that many anaesthetists may not be aware of this responsibility, nor of the fact that NMBAs can cross-react with other NMBAs allergenically.

The estimated incidence of anaphylaxis in Australia is between 1 in 10,000 and 1 in 20,000². Approximately

60% of cases of anaesthesia-related anaphylaxis are thought, on the basis of skin tests and epidemiological surveys, to be due to NMBAs^{3,4}.

If the patient in this report had been referred for formal allergy testing, the subsequent life-threatening reaction may have been avoided. When this patient was finally referred for testing, both vecuronium and suxamethonium tested positive. This means that the antibody that caused her reaction during the first anaphylactic reaction cross-reacted with both of these drugs. Although this had not been demonstrated at the time, to suggest that the cross-reactivity would not have been present initially is to argue that an entirely new and separate antibody had developed between the two episodes without exposure to either drug.

The cause of the anaphylaxis on repeat exposure was to either vecuronium, suxamethonium or both. From the anaesthetic record, both drugs were given on induction before any features of anaphylaxis were noted. Both drugs subsequently tested positive on intradermal testing. As such, determining which was the first to cross-link IgE and cause release of mediators from mast cells and basophils is not possible. Moreover, the distinction is of no clinical relevance as both were given before the reaction, both tested positive and both would need to be avoided along with rocuronium in future.

There is no evidence to suggest that anaphylaxis with more than one trigger simultaneously would be more severe than with a single trigger, as the same common pathway of degranulation would be initiated in either case.

In 2008 the Association of Anaesthetists of Great Britain and Ireland published revised guidelines on the management of anaphylaxis⁵. A key point is that, if anaphylaxis is suspected under anaesthesia, it is the anaesthetist's responsibility to ensure that the patient is referred for investigation. Suggested criteria for referral to a specialist centre for investigation includes unexpected hypotension (e.g. a mean arterial pressure decrease of ≥ 30 mmHg), which requires active treatment. Other criteria for referral include unexplained cardiac arrest during anaesthesia, unexplained bronchospasm (particularly if severe), widespread rash, urticaria or angioedema. A referral should detail all drugs given, a description of the reaction, copies of the anaesthetic, medication and recovery charts, relevant blood test results and the applicable timelines. The Association of Anaesthetists of Great Britain and Ireland guidelines also suggest that all departments of anaesthesia should identify a consultant anaesthetist who is the clinical lead for anaesthetic anaphylaxis⁵.

The diagnosis of anaphylaxis is made with intraoperative tests, e.g. mast cell tryptase and followed up with postoperative tests (including skin prick tests and/or intradermal tests) and sIgE testing for specific IgE antibodies⁶⁻⁹.

When anaphylaxis is suspected, the first blood sample (5 to 10 ml of clotted blood) for mast cell tryptase should be taken at the time of suspected anaphylaxis (but not delaying the resuscitation), ideally 40 to 60 minutes after the onset of the reaction. A second sample should be taken approximately four hours after the start of symptoms and a third sample at 24 hours or in convalescence (as a baseline level). The tryptase levels peak at 15 to 120 minutes and the half-life of tryptase is 1.5 to 2.5 hours¹⁰.

After suspected anaphylaxis, the patient must be fully informed, including a detailed written account of the episode. A letter confirming the diagnosis and outlining a plan for future anaesthesia should be sent to the patient and their general practitioner. Furthermore, the patient should be strongly advised to wear a medical warning bracelet or carry a medical warning card¹¹. The patient should be encouraged to ask any future anaesthetists to record all drugs administered on their allergy clinic information letter¹¹.

Cross-reactivity to more than one NMBA occurs in 84% of patients who are allergic to NMBAs and 16% of patients react to all in current use¹². Cross-reactivity is frequent among NMBAs because they share a common antigenic group, a quaternary ammonium ion, against which specific IgE antibodies are directed^{12,13}.

An uneventful exposure may sensitise an individual to subsequent administration of the drug³. In this case there was an uneventful anaesthetic for cholecystectomy in 2001 when rocuronium was used. Previous exposure to an NMBA, however, is not a prerequisite for an immunologically mediated anaphylactic reaction to an NMBA¹⁴. A history of previous exposure is found in fewer than 50% of patients who have had a reaction to an NMBA. It has been speculated that the origin of allergic sensitisation may include common environmental chemicals which share allergenic epitopes with the NMBAs, or another drug containing an ammonium ion¹⁵. Pholcodine, an anti-tussive agent found in cough medicines, is thought to cross-react with NMBAs and to sensitise exposed individuals¹⁶.

Further investigation of a suspected anaphylactic reaction is mandatory to find the responsible drug and to make future anaesthesia safer by avoiding all incriminated and cross-reacting compounds¹⁷. Only appropriately experienced clinicians should conduct

drug challenges¹³. Skin prick tests and intradermal tests can both be used for the diagnosis. At present, the overall performance and safety of skin tests makes them the most appropriate for diagnosis of NMBA-induced perioperative hypersensitivity reactions. If anaphylaxis to an NMBA is suspected, the patient should undergo skin testing with all the NMBAs commonly in use¹⁸, as cross-reactivity between NMBAs are common, in order to identify those NMBAs likely to be safe for future anaesthetics.

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