Histaminoid reactions associated with rocuronium

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We describe three histaminoid reactions occurring on induction of anaesthesia. The patients were all resuscitated successfully and subsequent skin testing suggested sensitivity to rocuronium. In this hospital, the incidence of such reactions is of the order of 1 in 3000. This may be coincidental but suggests that there should be close monitoring of the incidence of reactions to rocuronium. Review of the cases suggests that current guidelines on management are not always followed.


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Rocuronium is a monoquaternary aminosteroid neuromuscular blocking agent which first became available in 1994. Its main advantage is rapid onset, a dose of 0.6 mg kg⁻¹ producing block at the adductor pollicis muscle in 60–90 s. In common with vecuronium, another member of the aminosteroid group, rocuronium has been shown to cause less histamine release and cardiovascular instability than the benzylisoquinolinium neuromuscular blocking agents such as atracurium and mivacurium. However, it retains the potential to act as an antigen and three acute reactions have occurred in association with its use in our hospital in the past 2 yr. Skin testing suggested that each of these reactions was caused by rocuronium. We are aware of only one other published report, and therefore we felt it appropriate to draw attention to these cases and to review their management.

**Case reports**

**Patient No. 1**

A 58-yr-old woman was undergoing laparoscopic cholecystectomy after an episode of acute cholecystitis. She had a past history of palpitations for which she was receiving atenolol, although cardiological investigations, including a 24-h tape and exercise tolerance test, were negative. Previous general anaesthesia for a gynaecological procedure (thiopental 325 mg, atracurium 35 mg, morphine 7.5 mg, nitrous oxide, oxygen and enflurane) had been uneventful.

The patient was not premedicated. In the anaesthetic room, standard monitoring was commenced and i.v. access secured. Arterial pressure (non-invasive) was 100/46 mm Hg and heart rate 60 beat min⁻¹. The lungs were preoxygenated and anaesthesia was induced with morphine 5 mg i.v. and propofol 130 mg i.v. Rocuronium 40 mg was also given i.v. and, before intubation, the lungs were ventilated by hand with oxygen, nitrous oxide and isoflurane using a face mask, Guedel airway and a ‘Humphrey ADE’ circuit.

Some difficulty in lung ventilation was noted, with inflation pressures greater than expected being required to produce chest movement. A grade I view was obtained at laryngoscopy and the trachea was intubated with an 8-mm cuffed tracheal tube. The patient was noted to be generally erythematous, but with central cyanosis (oxygen saturation 86%) and an arterial pressure of 56/26 mm Hg. Auscultation of the chest revealed widespread wheeze.

Treatment for presumed anaphylaxis was commenced. The lungs were ventilated with 100% oxygen, epinephrine 1:10 000 was given i.v. in 1-ml increments (total 6 ml), and plasma protein solution (4.5% Alba) 800 ml i.v. was also given. Bronchospasm improved but methoxamine was given in 2-mg increments (total 20 mg) because the patient remained hypotensive and tachycardic. Chlorpheniramine 10 mg and hydrocortisone 200 mg were also given i.v. An arterial line, urinary catheter and an 8.5-French gauge right internal jugular venous line were inserted. Marked facial oedema was noted. Arterial blood-gas values revealed a pH of 7.19 with a base deficit of 9.7.

Fifty minutes after induction, the patient had stabilized with a heart rate of 99 beat min⁻¹, arterial pressure of 96/60 mm Hg and oxygen saturation of 98% on artificial
ventilation with 0.5% isoflurane in 100% oxygen. A total of 1600 ml of colloid and 2000 ml of crystalloid had been administered. The patient was transferred to the intensive care unit where she remained stable until the tracheal tube was removed 5 h later. Blood was analysed for serum tryptase 1 h after the reaction had occurred. Concentrations were increased at 95 ng ml⁻¹ (normal <1–2 ng ml⁻¹), confirming that mast cell degranulation had occurred.

The patient returned for skin testing 4 weeks later. Non-invasive monitoring (ECG, arterial pressure and pulse oximetry) was commenced, i.v. access secured and written consent obtained. Prick testing to normal saline, 1% propofol, morphine 1 mg ml⁻¹, succinylcholine 50 mg ml⁻¹ and atracurium 10 mg ml⁻¹ was uneventful. However, the patient complained of sensations of itch and burning almost instantly when rocuronium in 1:100 and 1:10 dilutions (0.1 mg ml⁻¹ and 1 mg ml⁻¹, respectively) were applied. A wheal <5 mm in diameter appeared in response to rocuronium 0.1 mg ml⁻¹, and one >5 mm in response to rocuronium 1 mg ml⁻¹. There was also a positive reaction to vecuronium, less intense than that to rocuronium. Subsequent administration of propofol, fentanyl, atracurium and morphine was uneventful.

**Patient No. 2**

A 29-yr-old woman with a history of hay fever for which she took no medication was undergoing laparoscopic sterilization. Her health was good and she had twice undergone uneventful general anaesthesia (atropine 0.6 mg, midazolam 2 mg, fentanyl 0.1 mg, propofol 100 mg, nitrous oxide, oxygen and enflurane; and fentanyl 0.05 mg, propofol 160 mg, nitrous oxide, oxygen and isoflurane) for minor surgical procedures in the past. Venous access was secured and standard monitoring instituted. Arterial pressure was 110/70 mm Hg and heart rate was 85 beat min⁻¹.

Anaesthesia was induced with propofol 170 mg, fentanyl 0.1 mg, glycopyrrolate 0.2 mg and rocuronium 15 mg. Manual ventilation with a face mask was performed with 1.5% isoflurane in 33% oxygen and 66% nitrous oxide. Some difficulty with ventilation and a tachycardia of 140–150 beat min⁻¹ were noted. A size 4 laryngeal mask airway was inserted as planned, but lung ventilation was difficult and auscultation of the chest revealed severe wheeze. The trachea was intubated with an 8-mm cuffed tracheal tube and manual ventilation was continued with 1% isoflurane in 100% oxygen. Within 3 min of induction, systolic arterial pressure was 45 mm Hg and SPO₂ 85%. An erythematous rash developed over the whole body, but was more pronounced in the lower half.

Hartmann’s solution 1 litre was infused rapidly and aminophylline 250 mg was given i.v., but bronchospasm improved only slightly. Therefore, epinephrine 0.3 mg was given slowly i.v., after which bronchospasm improved markedly. Plasma protein solution (Alba 4.5%) 2 litre was given over the next 30 min. Hydrocortisone 100 mg i.v. was also given. An arterial line was inserted and arterial blood-gas values showed a pH of 7.22 with a base deficit of 7.5. Arterial pressure improved to 90/50 mm Hg and SPO₂ to 100%. A further dose of epinephrine 0.2 mg was given slowly i.v. after which ventilation was improved and no wheeze was audible on auscultation of the chest. The proposed surgery was abandoned. Forty minutes after induction of anaesthesia, the patient was stable, making respiratory efforts and opening her eyes. The trachea was extubated soon after and the patient was monitored in the recovery area with no subsequent problems. Blood samples were obtained but were not analysed for serum tryptase as requested.

Six weeks later the patient returned for skin prick testing as described above. This was positive for both rocuronium (1:10 dilution) and vecuronium (1:10 dilution). There was no reaction to atracurium or succinylcholine. Subsequent administration of spinal anaesthesia with hyperbaric 0.5% bupivacaine 2.5 ml and fentanyl 0.025 mg i.v. was uneventful.

**Patient No. 3**

A 40-yr-old man who suffered from gastro-oesophageal reflux was admitted for elective endoscopic sinus surgery. He was otherwise healthy and his only medication was ranitidine. Previous anaesthesia with fentanyl 0.1 mg, thiopental 450 mg, vecuronium 10 mg, nitrous oxide, oxygen and enflurane had been uneventful. After venous access was secured and standard monitoring commenced, a modified rapid sequence induction was performed. The patient was given midazolam 2 mg, propofol 300 mg, fentanyl 0.1 mg and rocuronium 50 mg. The trachea was intubated with a 9-mm cuffed tracheal tube and the lungs ventilated with isoflurane in oxygen and nitrous oxide. He was noted to have a tachycardia of 175 beat min⁻¹ and to be markedly erythematous. Auscultation revealed wheeze throughout the chest, although oxygen saturation remained good throughout. Arterial pressure remained stable. Chlorpheniramine 10 mg and aminophylline 250 mg were given i.v. and bronchospasm improved. Surgery was postponed and the patient’s lungs were ventilated with isoflurane in oxygen and nitrous oxide until a spontaneous ventilatory pattern had been re-established. The tracheal tube was removed approximately 1 h after induction of anaesthesia when the patient was awake.

Four weeks later the patient returned for skin prick testing as described above. This was positive for rocuronium (1:10 dilution). There was no reaction to atracurium, vecuronium, succinylcholine, midazolam or propofol. Subsequent anaesthesia with propofol, atracurium, fentanyl, nitrous oxide, oxygen and isoflurane was uneventful.

**Discussion**

Anaphylaxis is a type 1 hypersensitivity reaction, mediated by IgE, in which a foreign substance produces an exaggerated immunological response leading to release of vasoac-
tive substances such as histamine and serotonin from basophils and mast cells. The clinical consequences of the release of these mediators may include pruritus, erythema, flushing, bronchospasm, hypotension and cardiovascular collapse. The term anaphylactoid is used to describe reactions that may be clinically indistinguishable from anaphylaxis but are not mediated by IgE. Clearly distinguishing between anaphylactic and anaphylactoid reactions is difficult, which is why we have used the term ‘histaminoid’.7

Estimates of the incidence of these reactions in anaesthesia vary from 1 in 350 to 700 in the UK,8 to 1 in 20 000 in Australia.9 Diagnosis may be difficult because the clinical features of an allergic reaction can be masked during anaesthesia, and cardiovascular instability or bronchospasm may be mistakenly attributed to other causes.3 Prompt treatment is essential, but fortunately it is primarily supportive, although an approach open to the possibility of misdiagnosis is required. Of the drugs used in anaesthesia, neuromuscular blocking agents are the most frequently implicated, accounting for approximately 70% of allergic reactions.10 Cross-reactivity between neuromuscular blocking agents is said to be common because of the ubiquitous quaternary ammonium group in these compounds, although rocuronium has been shown to exhibit less cross-reactivity than other neuromuscular blocking agents.11 However, only two of our patients had been exposed to a neuromuscular blocking drug previously (patient No.1 atracurium, patient No. 3 vecuronium), but two subsequently responded positively to vecuronium.

In all of our three patients the diagnosis of an histaminoid event was evident, each exhibiting the classical features of cardiovascular, respiratory and dermal involvement. They varied in severity, with patient Nos 1 and 2 being typical of moderately severe reactions, while the third was less severe. Treatment guidelines have been published by the Association of Anaesthetists12 and are available in all operating theatres in our hospital. Epinephrine is recommended as the mainstay of treatment but was given as a first-line drug in the treatment of only one of our patients. In patient No. 2, it was not given until bronchospasm had failed to respond to aminophylline. In the third case, which was less severe, none was given. This suggests that current guidelines were not followed; there was some reluctance to administer epinephrine even when the diagnosis of anaphylaxis was clearly suspected. In spite of this, all patients were treated successfully. This suggests that an expectant approach to treatment is not inappropriate in less severe cases, although our experience clearly supports the efficacy of epinephrine in severe cases. However, a drug with pure alpha agonist activity (methoxamine) was required in patient No. 1 to maintain arterial pressure and decrease heart rate, indicating the need for treatment to be matched to the clinical picture.

The guidelines from the Association of Anaesthetists recommend that the patient who has had a suspected anaphylactic reaction should be investigated in consultation with an allergist or a clinical immunologist. However, ready access to such specialists may, as in our hospital, be difficult, and skin testing was performed under the supervision of an anaesthetist with experience in its interpretation. It might be argued that any large centre should have an anaesthetist with this interest, because an anaesthetist has the appropriate skills to resuscitate the patient should skin testing precipitate a systemic response. An anaesthetist will also have a greater awareness of the other factors that may cause problems on induction of anaesthesia. Involvement of anaesthetists in testing should also increase awareness of the specifics of the process for the drugs used by the specialty. This is not irrelevant to this report. Having tested all of these patients, we found that there was some evidence that the ‘steroid’ neuromuscular blocking drugs should be tested in a dilution starting at 1:100, rather than the 1:10 dilution currently recommended.12 In two of these patients, we tested at a dilution no greater than 1:10, but 90% of ‘normal’ individuals are said to ‘respond’ to skin testing with rocuronium at this concentration (personal communication, Professor J. Levy). This may throw some doubt on the diagnosis in our patients, but all subsequently received anaesthesia without rocuronium in the same clinical setting without adverse effects. In two patients, the only difference in the anaesthetic technique was in the choice of neuromuscular blocking drug.

Based on the number of vials ordered from the hospital pharmacy, it is estimated that 8800 patients have received rocuronium in our hospital in the past 2 yr, giving an incidence of reaction to this drug of approximately 1:3000. In the same time period, no such reaction to any other neuromuscular blocking agent has been recognized. We are aware of only one other published case,7 but the Medicines Control Agency (personal communication) has been notified of eight and we are aware of another similar case in an associated hospital (personal communication, Dr E. Ritchie). We suggest that the frequency of reaction to this drug requires close monitoring.

References
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