

Case report

Early skin and challenge testing after rocuronium anaphylaxis

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Summary

We present a case of early skin and challenge testing in a patient following severe anaphylaxis to rocuronium. The patient presented for semi-elective laparoscopic cholecystectomy and developed anaphylaxis with severe cardiovascular collapse after induction of anaesthesia. Surgery was cancelled but was considered necessary before the recommended four to six weeks for formal allergy testing. Limited skin and challenge testing was performed to rocuronium and cisatracurium while the patient was in the intensive care unit to identify a safe neuromuscular blocking drug for subsequent early surgery. The subsequent surgery, 48 hours after the initial reaction, was uneventful. The case highlights the difficulties when anaesthetising patients with recent anaphylaxis who have not yet had formal allergy testing and presents a potential management strategy involving early skin testing.

Key Words: anaesthesia, anaphylaxis, rocuronium, neuromuscular blocking agents, remifentanyl

This case report addresses an area of anaesthetic practice where there is uncertainty and a lack of standard guidelines. The potential for early skin and challenge testing post suspected anaphylaxis to provide clinically useful information prior to urgent surgery may allow the anaesthetist to proceed with greater confidence with the risk to the patient minimised.

A 17-year-old female with no other significant medical history presented for semi-elective laparoscopic cholecystectomy. Patient consent for this report was obtained. Her only past anaesthesia was a recent uncomplicated endoscopy for which she had received sedation with fentanyl, midazolam, and propofol.

A cannula was inserted after skin preparation with a chlorhexidine/alcohol swab and midazolam was administered in the anaesthetic room before the patient was brought into the operating theatre. Induction of anaesthesia was with fentanyl and propofol; rocuronium was administered for muscle relaxation, and anaesthesia was maintained with sevoflurane in oxygen. No antibiotics were given. Within one minute of administration of rocuronium, bag-mask ventilation became extremely difficult despite insertion of a Guedel airway, and the patient developed tachycardia (up to 150 /minute). At this time the non-invasive systolic blood pressure measured 65 mmHg and a generalised rash was developing. The patient was immediately intubated without difficulty. A presumptive diagnosis of anaphylaxis was made

and extra medical and nursing assistance was summoned.

Over the next 20 minutes, IV adrenaline boluses of 100 µg to a total of 1.2 mg were administered via peripheral lines, but the patient remained profoundly hypotensive with unrecordable cuff pressures and absent radial pulses, although a strong carotid pulse was palpable. Additional IV access was obtained with a peripheral cannula and an internal jugular central venous catheter and infusions of adrenaline (10 µg/minute) and noradrenaline (6 µg/minute) were commenced. A femoral arterial line was inserted and a systolic blood pressure of 100 mmHg was achieved after approximately 30 minutes with these inotropes and rapid infusion of six litres of compound sodium lactate. Despite the patient appearing oedematous, transthoracic echocardiography during resuscitation showed a hyperdynamic left ventricle with reduced cavity area.

Surgery was cancelled and she was transferred intubated to our intensive care unit (ICU). After 24 hours in ICU, inotropes were weaned although she remained intubated because of her oedematous state.

As a result of the surgery having been deferred, her treating team and family were faced with a difficult dilemma: her frequent significant symptoms could precipitate hospital presentation and the need for urgent surgery prior to formal skin testing that would be undertaken at four to six weeks. Additionally, the patient was soon to have final school exams, and her family desired that her illness be resolved as quickly as it was safe to do so.

The following day, while the patient remained sedated, intubated and ventilated in ICU (without the use of muscle relaxants), limited intradermal skin testing was performed to identify a safe neuromuscular blocking drug in anticipation

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of laparoscopic cholecystectomy. Rocuronium was tested as the likely causative agent and cisatracurium as a possible alternative, should muscle relaxation be required for the proposed surgery. Intradermal injections of saline (negative control), 1:1000 morphine (positive control), 1:1000 rocuronium and 1:1000 cisatracurium were performed (Figure 1). Due to the oedematous condition of her skin no wheals developed, but there were flare responses to both the morphine positive control and rocuronium, while there were no responses to either saline or cisatracurium. The rocuronium response was interpreted as positive and the cisatracurium as negative. In view of the limitations of skin testing she then underwent a cisatracurium intravenous challenge: 1 ml of 10-fold increasing concentrations of cisatracurium, commencing at 1:1000 through to 2 mg neat cisatracurium, with no adverse effects.



Figure 1: Intradermal skin testing results. S = saline (negative control), R = rocuronium, C = cisatracurium, M = morphine (positive control). Flush only with no wheal noted to rocuronium considered a positive result.

While still sedated and intubated, the patient was taken to theatre 48 hours after the episode of anaphylaxis for laparoscopic cholecystectomy. Anaesthesia was maintained with sevoflurane and a remifentanyl infusion. A fentanyl infusion from ICU was left running at 20 µg/hour, and a noradrenaline infusion was commenced prophylactically. A single dose of ceftriaxone was also administered. Although the cisatracurium challenge had been negative, it was not administered as the consultant surgeon reported adequate

surgical conditions without muscle relaxation. An inflamed, oedematous gallbladder was removed. The patient remained intubated for 24 hours before uneventful extubation and subsequent discharge from ICU and recovery on the ward.

Approximately ten weeks following discharge, formal allergy testing was undertaken. The patient had a positive reaction (wheal and flare) to rocuronium, pancuronium and vecuronium. This, together with a raised specific IgE to quaternary ammonium, was evidence of an allergic reaction to rocuronium, and cross-sensitivity to the muscle relaxants pancuronium and vecuronium. Skin testing to all other agents was negative, including the benzylisoquinoline neuromuscular blocking drugs atracurium and cisatracurium.

Discussion

The decision to abandon surgery after anaphylaxis may be difficult. In this case, initial incision had not been made and considering the profound cardiovascular collapse and significant support required, deep anaesthesia and pneumoperitoneum would have been undesirable. Moreover, further reactions may have been triggered if additional doses of neuromuscular blocking drugs were required to facilitate surgery. Certainly, with less severe reactions that rapidly respond to adrenaline, it may be reasonable to continue with surgery, especially if it is deemed urgent. In contrast, severe reactions are associated with prolonged cardiovascular instability and require large doses of inotropes and large volumes¹⁻³ of intravenous fluid, as in our case.

This case highlights a dilemma anaesthetists may face when managing patients who require semi-urgent or emergency surgery following anaphylaxis during anaesthesia. Formal skin testing is generally recommended to occur at least four to six weeks after the initial reaction has occurred^{4,5}. The rationale for this is that early testing may result in false negatives due to depletion of mediators from mast cells and basophils (e.g. histamine) after the initial reaction⁴. However, the necessity to delay skin testing has recently come into question. The British Society for Allergy and Clinical Immunology have stated in their 2010 guidelines for investigation of anaphylaxis during anaesthesia that “there is no reason to delay after the allergic reaction, and this can be considered as soon as the patient has recovered from the reaction and the effects of the drugs used to treat anaphylaxis”⁶. A similar statement has been made by the Association of Anaesthetists of Great Britain and Ireland¹. This is in contrast to previous recommendations and a reason for the change is not clear. Others have suggested that only positive results from early skin testing should be taken into account⁵.

Soetens et al⁵ reviewed a series of case reports of skin testing performed within three weeks of the initial suspected anaphylactic reaction. They reported eight patients who had a positive skin test within three to 14 days of suspected reaction. However there were three cases of negative skin

testing shortly after the reaction that became positive at a later time.

Lafuente et al⁴ conducted a prospective study of all suspected anaphylactic reactions over a four-year period in their hospital. Skin testing was performed between 0 to four days after the reaction and again four to eight weeks later. Forty-four patients were included in the study. Twenty-five patients had positive skin tests of which 15 were positive early and 22 later. Therefore three patients were positive only early while 10 were positive only later. They concluded that the moderate strength of agreement between early and late testing seems to justify early testing but that it could not be considered a replacement for later testing.

Clearly, this is an area that needs more research. Currently there do not seem to be any clear guidelines on management and investigation for urgent surgery in the setting of recent suspected anaphylaxis and this would certainly be useful for anaesthetists. If surgery cannot be postponed, Soetens et al⁵ have a suggested protocol for managing such cases which only recommends early skin testing if muscle relaxation is necessary for the procedure. Unfortunately safe alternative neuromuscular blocking drugs cannot be selected without testing, due to the high incidence of cross-sensitivity which is not always class-specific. Therefore only a drug that has tested negative and has a different chemical structure (benzylisoquinoline or aminosteroid) should be used. However, if muscle relaxation is deemed unnecessary then surgery can proceed without skin testing but with precautions, including avoiding latex, avoiding penicillins and cephalosporins (if used previously), switching to another antiseptic (chlorhexidine or povidone iodine) and where possible using a different anaesthetic technique such as regional or inhalational anaesthesia. Specific IgEs may also be measured but the results should be interpreted with caution.

A second consideration in this case was whether it would be possible surgically to perform the postponed laparoscopic cholecystectomy without neuromuscular blocking drugs. Therefore, due to the uncertainty regarding the validity of negative early skin testing, an intravenous challenge test was also performed in a controlled environment prior to surgery to identify a potentially safe drug. Despite this, it was felt that the safest initial approach was still the avoidance of a neuromuscular blocking drug. However, should it have been required for completion of surgery, cisatracurium would have been administered. Blobner et al⁷ performed a randomised controlled trial comparing laparoscopic cholecystectomies performed with and without muscle relaxant. In their study anaesthesia was induced with propofol and fentanyl and maintained with desflurane and remifentanyl and patients were randomised to no muscle relaxant or rocuronium to maintain deep neuromuscular blockade. Of the 50 patients included in the results, 25 received no neuromuscular blockade and during 12 of these cases, at least one adverse

advent was recorded, most commonly inadequate surgical visibility at an intra-abdominal pressure of 15 mmHg requiring a bolus of muscle relaxant. Time of surgery and postoperative outcomes were the same in both groups. While this study shows a significant improvement in surgical conditions with the use of muscle relaxant, it also highlights that relaxant is not always required and that patient outcomes are not altered by their avoidance. As an extremely potent and easily titratable opioid, remifentanyl may be a good alternative when aiming to avoid neuromuscular blocking drugs for surgery where they are typically required.

This case demonstrates a limited role for early skin testing post anaphylaxis. A positive test enables unsafe drugs to be avoided. A negative test may be followed by a progressive challenge to clarify the safety of an alternative drug, but no standard practice currently exists.

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