

Neostigmine anaphylaxis: A rare and missed diagnosis

Alan J McKenzie 

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This is a report of a moderate anaphylactic reaction confirmed by tryptase rise and skin testing to have been caused by neostigmine, a very rarely reported diagnosis. It seems likely this patient had three previous reactions to neostigmine missed by her attending anaesthetists. Anaphylactic reactions occurring in the final phases of anaesthesia care may be missed or misdiagnosed for a number of reasons.

The patient gave consent for this report to be submitted for publication. A 67-year-old woman, height 161 cm, weight 97 kg, with hypertension treated with an angiotensin converting enzyme inhibitor (ACEI) and beta blocker, presented for laminectomy and bilateral discectomy at L3–4 vertebrae level. She had been told not to take her ACEI on the morning of surgery, but her beta blocker had been taken as usual.

Following placement of standard monitoring including non-invasive blood pressure, general anaesthesia was induced with propofol, remifentanyl infusion and sevoflurane. After muscle relaxation with atracurium 30 mg, intubation and urinary catheter placement were performed and the patient was turned prone on a spine surgery table. Prophylactic cefazolin 3 g was administered. Dexamethasone 8 mg and droperidol 0.75 mg were given as emesis prophylaxis. A phenylephrine infusion was commenced at 0.4 µg/kg/min to maintain stable mean arterial pressure around 80 mmHg. The heart rate was also steady in the mid-50s, reflecting the patient's beta blockade. Surgery was completed. The surgeon placed an epidural catheter, aspiration-test negative single-shot epidural analgesia with 0.375% ropivacaine 6 ml, fentanyl 30 µg and morphine 3 mg was given, then the catheter was removed. Wound closure commenced immediately and simultaneously, around 75 minutes after the initial and only atracurium dose, premixed neostigmine 2.5 mg/glycopyrrolate 0.5 mg was given.

By three minutes after reversal, despite the beta blockade, her heart rate was 110 per minute. The next 2.5-minute frequency cuff blood pressure was unrecordable. The pressure-controlled mode ventilator flow and pressure tracings appeared to show the patient coughing, with reduced tidal volumes. The patient's

hands and forearms, the only easily visible parts of her body given the draping, were very pale and there was delayed capillary refill. Pulse oximetry waveform was low amplitude and of poor quality. End-tidal carbon dioxide levels remained essentially unchanged.

The surgical team were alerted and closure expedited. Phenylephrine was repeatedly bolused and the infusion rate rapidly increased. A transient desaturation percentage to the mid-70s was recorded by the automated recording system. Sevoflurane washout commenced and the fresh gas flow was changed to 100% oxygen. Ten minutes after the initial recognition that something untoward was occurring, the patient was supine in her ward bed, mean arterial pressure around 60 mmHg, heart rate around 85 per minute, oxygen saturations 99%. Peripheral perfusion in her arms and the saturation plethysmograph improved markedly as she was moved from the prone 'surrender position' to supine with her arms by her side. She was breathing well spontaneously, was able to be extubated and transferred to the post-anaesthesia care unit (PACU). On examination there was no sign of a 'spinal' type neuraxial block, the patient could move her legs on command with normal power and she was comfortable. Phenylephrine requirements decreased relatively quickly and she was transferred to the ward on no specific treatment within three hours of PACU arrival.

Serial tryptase samples were taken, soon after arrival in PACU, around three hours post reaction, and the following morning. The tryptase sequence in chronological order was 27.2, 16.3 and 4.7 µg/ml, lab normal <11.5 µg/ml.

Capital and Coast District Health Board, Wellington Regional Hospital, Wellington, New Zealand

Corresponding author:

Alan James McKenzie, Capital and Coast District Health Board, Wellington Regional Hospital, Adelaide Road, Wellington 7902, New Zealand.

Email: alan.mckenzie@ccdhb.org.nz

Intradermal testing was performed around six weeks post event by a member of the Australian and New Zealand Anaesthetic Allergy Group. Negative and positive control prick tests showed normal skin reactivity. Negative tests were recorded for glycopyrrolate, lidocaine, ropivacaine, cefazolin, atracurium, midazolam, fentanyl, propofol, morphine, dexamethasone, droperidol and chlorhexidine. A positive test was recorded for neostigmine at 1/1000 dilution.

The patient had provided a history of five general anaesthetics, three at another hospital, since 1999. Hard copy medical records for these three anaesthetics were able to be obtained by the time of intradermal testing:

1999: Breast cancer, wide excision and axillary clearance. Rocuronium relaxation and neostigmine/glycopyrrolate reversal. No PACU record was available but 'Haemaccel 500 ml given stat in PACU' was noted on the anaesthesia record.

2012: Multiple skin lesions including on the patient's back. Rocuronium relaxation and neostigmine/glycopyrrolate reversal. Systolic blood pressure pre reversal was around 130 mmHg. The next blood pressure was 90 systolic and nadir 15 minutes later at 65/30. Recorded metaraminol of a total 4 mg was given with 500 ml of Haemaccel.

2014: Laparoscopic cholecystectomy. Rocuronium relaxation and neostigmine/glycopyrrolate reversal. The time of reversal was recorded. The last blood pressure recording was five minutes prior, the next recording 20 minutes later. Recorded 2 mg metaraminol was given in between.

The tryptase rise and positive skin test confirmed anaphylaxis to neostigmine, which has been reported rarely.¹ A 2019 review of anaesthetic associated anaphylaxis epidemiology failed to mention neostigmine as a potential trigger. The same review estimated the anaphylaxis rate with sugammadex use at 0.04%.² The NAP 6 report recorded no anaphylactic events attributed to neostigmine and recorded it as only rarely being reported.³ The reversal of neuromuscular blocking agents with sugammadex appears much more likely to cause anaphylaxis than reversal with neostigmine.

Although it cannot be proved, it is possible this patient had moderate anaphylactic reactions to neostigmine in three previous anaesthetics, which were treated symptomatically but not investigated as potential anaphylaxis. The incomplete manual records available to us make definite post-event analysis impossible.

It would seem likely that significant anaphylaxis to neostigmine is rare, given the length of time the drug has been in use and the lack of case reports confirmed by tryptase rise and skin testing. But given (a) the timing of administration, (b) the frequent reduction in monitoring soon after administration, (c) the frequently poor recording of vital signs in the transition to the PACU, (d) that hypotension post anaesthesia is more commonly due to blood loss or residual neuraxial block, and (e) the lack of awareness of neostigmine's potential as a trigger, the true incidence can only be guessed.

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ORCID iD

Alan J McKenzie  <https://orcid.org/0000-0001-8163-7051>

References

1. Seed MJ and Ewan PW. Case report: Anaphylaxis caused by neostigmine. *Anaesthesia* 2000; 55: 574–575.
2. Mertes PM, Ebo DG, Garcez T, et al. Comparative epidemiology of suspected perioperative hypersensitivity reactions. *Br J Anaesthesia* 2019; 123: e16–e28.
3. Harper NJN. Neuromuscular blocking agents and reversal agents. In: Cook TM and Harper NJN (eds) *NAP 6 Report: Anaesthesia, Surgery and Life-Threatening Allergic Reactions*. London: Royal College of Anaesthetists. 2018, pp. 192–196.