Anaesthesia, 2000, **55**, pages 574–575

CASE REPORT

Anaphylaxis caused by neostigmine

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Summary

A patient developed anaphylaxis during anaesthesia, towards the end of surgery, 30 s after intravenous administration of neostigmine. Anaphylaxis to neostigmine was confirmed by demonstrating an elevated mast cell tryptase and a strongly/positive skin prick test, showing the presence of drug-specific IgE (skin prick tests to neostigmine were negative in normal subjects). This is a rare cause of anaphylaxis during anaesthesia.

Keywords *Anaphylaxis*: neostigmine.

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Accepted: 15 June 1999

Anaphylaxis is an increasing problem and may occur during anaesthesia [1–3]. Anaphylaxis is a severe systemic allergic reaction, mediated by specific IgE antibody. The term anaphylactoid reaction is used for a reaction clinically similar to anaphylaxis, but where the mechanism is different and IgE antibody is not involved. In France, the incidence of anaphylactic or anaphylactoid reactions during anaesthesia is 1 in 3500 and for anaphylaxis (reactions shown to be IgE-mediated) 1 in 6000 [4, 5]. Data from 1990 to 1991 show that most of the anaphylaxis associated with anaesthesia is due to neuromuscular blocking drugs [5], but recent studies show that latex rubber allergy is now accounting for an increasing proportion. This is the first report of a case of anaphylaxis due to neostigmine, providing confirmatory evidence of the aetiology.

Case history

A 64-year-old woman was admitted for a breast lump excision after calcification had been found on a routine mammogram. Her surgical history comprised an appendicectomy (aged 29) and hysterectomy (aged 45). She also had a history of depressive illness, hiatus hernia and an inferior wall myocardial infarction 10 years previously. She was taking the following medication: Premarin, omeprazole, paroxetine, lorazepam and quinine sulphate. She had a history of mild hayfever but no other manifestations of atopy. There was no history of latex rubber allergy.

Because of her hiatus hernia with oesophageal reflux, rapid sequence induction was used. She was pre-oxygenated and anaesthesia was induced with midazolam 1.5 mg, fentanyl 100 μg, propofol 150 mg, succinylcholine 75 mg and intubated following application of cricoid pressure. Neuromuscular paralysis was maintained with atracurium. Anaesthesia was maintained with nitrous oxide, oxygen and enflurane.

Surgery proceeded uneventfully and was complete within approximately 30 min. For reversal of neuromuscular blockade, 1 ml of glycopyrronium (0.5 mg)/neostigmine (2.5 mg) (Robinul-Neostigmine) was administered intravenously. Thirty seconds later, the patient developed a generalised rash, bronchospasm, peri-orbital oedema and became bradycardic with an unrecordable blood pressure. Oxygen saturation diminished to 60%. Ephedrine 12 mg was administered intravenously, followed by chlorpheniramine 10 mg, hydrocortisone 100 mg and epinephrine 150 μg (1.5 ml of 1 : 10 000). The patient subsequently had episodes of supraventricular tachycardia requiring treatment with adenosine. She was kept on the intensive care unit overnight but quickly stabilised and was discharged 3 days later.

The serum mast cell tryptase level 4 h after the reaction was 37.6 ng.ml^{-1} (normal range 2–14 ng.ml^{-1}). Skin prick tests were positive to neostigmine (wheal diameter 9 mm for drug at stock concentration (2.5 mg.ml^{-1}); wheal diameter 7 mm with 1 in 10 dilution). Skin tests were negative to the anaesthetic drugs glycopyrronium,

propofol, succinylcholine, atracurium and fentanyl (tested at both stock concentrations and 1 in 10 dilutions), and to latex rubber. Her total serum IgE level was 171 $IU.l^{-1}$ (normal range 10–170 $IU.l^{-1}$). Specific IgE (CAP-RAST, Pharmacia) to latex rubber was negative. The skin prick test to edrophonium tested at stock concentration (10 $mg.ml^{-1}$) and 1 in 10 dilution was negative. Skin prick tests with neostigmine (both stock concentration and 1 in 10 dilution) were negative in 20 healthy volunteers.

Discussion

This patient had an anaphylactic reaction to intravenous administration of neostigmine. The clinical features and the time to onset of the reaction were typical of anaphylaxis to an intravenous drug, which usually occurs within a minute of administration [2, 3]. The time of onset indicates the cause, ruling out the induction agents and being highly suggestive of neostigmine. Mast cell mediator release was confirmed by demonstration of the elevated tryptase, but this does not differentiate between different causes of mast cell activation, e.g. an IgE-mediated reaction or direct effects of a drug. That the reaction was mediated by neostigmine-specific IgE was shown by skin prick testing, which showed an unequivocal strong positive in the patient and completely negative results in controls.

Latex rubber allergy causes intra-operative anaphylaxis (as opposed to the induction agents which cause anaphylaxis before the start of surgery) as there is a delay between exposure and onset while the allergen is absorbed [3]. This was unlikely on history, because of the timing, severity and speed of onset of the reaction, suggesting neostigmine as a cause. Further, there was no history of preceding latex sensitivity. Although this was most unlikely to be the cause, the negative latex rubber IgE ruled this out.

Whilst anaphylaxis to other drugs used during anaesthesia is well recognised, these are mainly due to the neuromuscular blocking agents, e.g. suxamethonium, vecuronium or atracurium [5, 6]. In France, muscle relaxants were responsible for 70% of 813 cases of anaphylaxis during anaesthesia, suxamethonium accounting for the majority [5]. Neostigmine is an anticholinesterase drug, frequently used for reversal of nondepolarising neuromuscular blockade. Only one case of anaphylaxis due to neostigmine is mentioned in the literature, but the only information given was in a table stating that neostigmine was the cause of one of a series of 443 cases of anaphylaxis during anaesthesia [6].

We believe this to be the first case report with data confirming neostigmine to be the cause of the anaphylactic reaction, by demonstrating neostigmine-specific IgE. It is important that anaesthetists are aware of the potential allergenicity of neostigmine. In order to establish whether another anticholinesterase could be used, skin prick tests to edrophonium were performed, and showed no evidence of specific-IgE, suggesting this drug would be safe for future use.

Acknowledgment

We are grateful to Mr W. A. B. Smellie for referring this case.

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