CASE REPORTS

Failure to prevent an anaphylactic reaction to a second neuromuscular blocking drug during anaesthesia

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Skin testing is used widely to determine the drug responsible for an anaphylactic reaction during anaesthesia. When a neuromuscular blocking drug is incriminated as the cause of a reaction, it is usual for neuromuscular blocking drugs which do not produce positive skin tests to be considered safe for subsequent use during anaesthesia. We describe three patients in whom false negative skin tests led to a second severe anaphylactic reaction to another neuromuscular blocking drug.

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Case reports

Patient No. 1

A 23-yr-old woman with a history of allergy to penicillin and sulphonamides and a previous uneventful anaesthetic where thiopental was the sole agent used, was anaesthetized in 1981 for dilatation and curettage. She was given thiopental and decamethonium, and developed hypotension, tachycardia and cyanosis. She was resuscitated over 90 min with hydrocortisone, Ringer’s lactate and 5% stable plasma protein solution (SPPS). Intradermal testing was performed 1 month later and showed a clear-cut positive response to decamethonium and negative responses to succinylcholine, gallamine and thiopental.

Five months later she was anaesthetized for removal of wisdom teeth. She was given test doses of 0.05 ml of thiopental 25 mg ml⁻¹, succinylcholine 50 mg ml⁻¹ and gallamine 40 mg ml⁻¹ at 2-min intervals with no adverse response. Anaesthesia was induced with gallamine 30 mg, thiopental 350 mg and succinylcholine 100 mg i.v., and a 6.5-mm Rusch nasotracheal tube was inserted. Within minutes, swelling, hypotension (systolic arterial pressure
85 mm Hg) and tachycardia occurred. She was given gallamine 120 mg. Arterial pressure continued to decrease and three doses of epinephrine 100 μg were given followed by Ringer’s lactate 500 ml and SPPS 500 ml. Arterial pressure was stable within 25 min. A flushed appearance was noted.

She was re-tested intradermally 1 month later and showed positive skin tests to decamethonium and succinylcholine, and negative tests to thiopental, gallamine, alcuronium, pancuronium and tubocurarine. A group of four other patients allergic to succinylcholine were tested with decamethonium and all were positive. It was assumed that there had been an error in skin testing.

In 1985, her serum obtained in 1981 was tested by RIA and she showed positive tests to all the blockers tested, including alcuronium (14.5), succinylcholine (17.5), gallamine (10.6), tubocurarine (23.4) and vecuronium–pancuronium (3.8). (Results of RIA tests are expressed as percentage uptake of $^{125}$I labelled anti-IgE. The upper limit of normal is three times uptake in control baseline and is usually approximately 3; the same RIA is used to detect antibodies to pancuronium and succinylcholine.)

Over the subsequent 12 yr, she has been tested intradermally on four occasions and shown one negative test to decamethonium, three negative and one positive tests to succinylcholine and negative tests to tubocurarine, alcuronium, gallamine, pancuronium, atracurium and vecuronium. In 1998 she tested positive to succinylcholine and mivacurium and negative to atracurium, pancuronium, vecuronium and rocuronium. She has not had an anaesthetic using a neuromuscular blocking drug since 1981.

**Patient No. 2**

A 30-yr-old male with a history of allergy to grasses was referred in 1990 before anaesthesia for dental extraction. He had a note from a French anaesthetist stating that in 1989 he had developed anaphylaxis after thiopental, fentanyl and pancuronium. Intradermal and prick testing showed a strong positive response to pancuronium and succinylcholine, an equivocal response to vecuronium, and negative responses to tubocurarine, alcuronium, thiopental and fentanyl. The intradermal test but not the prick test was positive for atracurium, which suggested it may have been a false positive test caused by cutaneous histamine release. Histamine responsiveness was normal. The patient was given a letter suggesting that alcuronium was the drug of choice for subsequent anaesthesia.

In 1994, he was anaesthetized for dental extractions. He was given a test dose of alcuronium 0.5 mg followed at 1-min intervals by dexamethasone 8 mg, propofol 170 mg with lidocaine 40 mg, and alcuronium 20 mg. Within 4 min he was observed to have ‘cadaveric pallor and cyanosis’ and his heart rate increased to 125 beat min$^{-1}$, systolic arterial pressure was less than 50 mm Hg and arterial saturation was only 70%. He was given 4 ml of epinephrine 1:10 000 i.v. and Haemaccel 500 ml. Within 5 min, systolic arterial pressure was 115 mm Hg. Blood obtained 1 h after the reaction commenced showed a mast cell tryptase concentration of 15 iu ml$^{-1}$ (normal value less than 2 iu ml$^{-1}$). RIA testing showed positive tests to succinylcholine (16.6) vecuronium (5.4) and morphine (25.6), and negative tests to alcuronium (2.5) and thiopental (1.6).

Intradermal testing was repeated 1 month after the reaction. Histamine responsiveness was normal. He showed positive intradermal tests to succinylcholine, pancuronium and vecuronium, negative tests to thiopental and propofol, an equivocal test to alcuronium and a negative test to atracurium. His current warning letter suggests that if a neuromuscular blocking drug is necessary, atracurium would be the drug of choice but neuromuscular blocking drugs would best be avoided and pretreatment should be considered. He has been invited to return for leucocyte histamine release tests and for testing to newer neuromuscular blocking drugs but has declined.

**Patient No. 3**

A 50-yr-old female was anaesthetized for vaginal hystereotomy. She gave a history of allergy to morphine, penicillin, amoxycillin and furadantin. She had a past history of four general anaesthetics and one spinal anaesthetic but no records were obtainable. It is likely that neuromuscular blocking drugs were used in the four general anaesthetics given between 1958 and 1983. After administration of pethidine 50 mg, droperidol 1 mg, midazolam 2 mg, ondansetron 4 mg, propofol 200 mg and rocuronium 60 mg, she developed flushing, cyanosis and profound hypotension requiring external cardiac compression, epinephrine 1.5 mg, Ringer’s lactate 1 litre and Haemaccel 1 litre. Arterial pressure could be recorded at 20 min and was normal by 50 min. Mast cell tryptase concentration was 107 iu ml$^{-1}$ at 4 h (normal less than 5 iu ml$^{-1}$) and RIA tests on blood obtained at the time of the reaction showed positive tests for morphine (32.2) and succinylcholine (21.4) and negative tests for vecuronium–pancuronium (0.4), rocuronium (0.3) and atracurium (1.1). The tests for alcuronium (2.9) and thiopental (3.8) were equivocal.

Intradermal testing carried out 1 month later showed negative tests to midazolam, propofol, ondansetron, pethidine, droperidol, fentanyl, atracurium, mivacurium, vecuronium and morphine, and positive tests to rocuronium and succinylcholine.

She was anaesthetized 2 months later with pethidine, droperidol, propofol and vecuronium and developed an identical reaction* which responded to epinephrine 2 mg and

*The skin tests were repeated by Dr B. Maycock 4 months after the second reaction using the same dilutions but the back rather than the forearm. There were strong positive tests to rocuronium, succinylcholine, vecuronium, pancuronium, and negative responses to atracurium, mivacurium and cisatracurium. Two weeks later she was uneventfully anaesthetised using spinal anaesthesia.
Ringer’s lactate 2 litre. Arterial pressure returned to normal at 30 min.

Discussion

Skin testing, whether intradermal or prick testing, is the most useful method of determining the drug responsible for anaphylactic reactions during anaesthesia, with the exception of colloid solutions or contrast media. In our series, skin testing failed to detect a cause in approximately 20% of patients with a suspected anaphylactic reaction. However, the test is much more specific when used in patients in whom an anaphylactic cause is confirmed by elevated mast cell tryptase concentrations.

Uneventful subsequent anaesthesia after anaphylactic reactions is likely when intradermal and RIA testing negative drugs are used and the drug responsible has been detected. In 337 patients, of whom we have received information regarding subsequent anaesthesia, 329 have had an uneventful anaesthetic. Of 192 patients who reacted to neuromuscular blocking drugs, 185 have had subsequent uneventful anaesthesia, including 176 who received a skin-test-negative drug uneventfully. Two other patients had second reactions to neuromuscular blocking drugs for which they were not tested as the problem occurred before our awareness of cross-sensitivity. One other had a minor reaction to a skin-test-negative drug and another who was allergic to atracurium developed profound bradycardia and hypotension after thiopental, fentanyl and vecuronium, allergic to atracurium may represent a newly acquired sensitivity. The other patient had a second reaction to a skin-test-negative drug and another who was allergic to atracurium developed profound bradycardia and hypotension after thiopental, fentanyl and vecuronium, which was not thought to be anaphylactic.

The three patients described here represent the only three that have reacted to a skin-test-negative drug when a cause for the previous reaction was established. Leynadier, Calinaux and Dry described 16 of 27 known patients with a positive skin test to one neuromuscular blocking drug after an anaphylactic episode, who received a second skin-test-negative neuromuscular blocking drug uneventfully. Cross-sensitivity between neuromuscular blocking drugs has been shown in patients who have reacted to more than one neuromuscular blocking drug and who was allergic to atracurium developed profound bradycardia and hypotension after thiopental, fentanyl and vecuronium, which was not thought to be anaphylactic.

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Bouaziz and Laxenaire suggested that skin testing should be repeated before anaesthesia if the investigations were done 2–3 yr previously as new sensitivities may have been acquired. Two patients in this study had second reactions within this time period. It is likely that these results represented false negative skin tests rather than newly acquired sensitivities. The other patient had a second reaction 4.8 yr after the first, and the equivocal skin test to alcuronium may represent a newly acquired sensitivity.
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