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Anaphylaxis to neuromuscular blocking drugs: incidence and cross-reactivity in Western Australia from 2002 to 2011

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Editor's key points

- Neuromuscular blocking drugs (NMBDs) are common triggers of anaphylaxis in anaesthesia.
- Rocuronium may be associated with a higher incidence when compared with other NMBDs.
- After accounting for usage rate, rocuronium had a three-fold increased risk of IgE-mediated anaphylaxis compared with vecuronium.

Background. Neuromuscular blocking drugs (NMBDs) are the most common cause of intraoperative anaphylaxis in Western Australia. Differences in the rates of anaphylaxis between individual agents have been surmised in the past, but not proven, and are an important consideration if agents are otherwise equivalent.

Methods. We estimated a rate of anaphylaxis to NMBDs by analysing cases of NMBD anaphylaxis referred to the only specialized diagnostic centre in Western Australia over a 10 yr period. Exposure was approximated by analysing a 5 yr period of NMBD ampoule sales data. Agents were also ranked according to the prevalence of cross-reactivity in patients with previous NMBD anaphylaxis.

Results. Rocuronium was responsible for 56% of cases of NMBD anaphylaxis, succinylcholine 21%, and vecuronium 11%. There was no difference in the severity of reactions for different NMBDs. Rocuronium had a higher rate of IgE-mediated anaphylaxis compared with vecuronium (8.0 *vs* 2.8 per 100 000 exposures; $P=0.0013$). The prevalence of cross-reactivity after NMBD anaphylaxis suggested that succinylcholine also has a high risk of triggering anaphylaxis. Cisatracurium had the lowest prevalence of cross-reactivity in patients with known anaphylaxis to rocuronium or vecuronium.

Conclusions. Rocuronium has a higher rate of IgE-mediated anaphylaxis compared with vecuronium, a result that is statistically significant and clinically important. Cisatracurium had the lowest rate of cross-reactivity in patients who had previously suffered anaphylaxis to rocuronium or vecuronium.

Keywords: anaphylaxis; cross-reactivity; neuromuscular blocking drugs; rocuronium

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Intraoperative anaphylaxis is a rare and unpredictable event, but nonetheless a significant problem as it is complicated by significant morbidity and a reported mortality of between 3.5% and 10%.[1] The class of drugs most commonly implicated are the neuromuscular blocking drugs (NMBDs). Clinically important questions with respect to NMBD anaphylaxis include the following. First, which NMBD—satisfying the various requirements of onset, duration, and reversibility—is the least likely to cause anaphylaxis in routine practice? Secondly, what is the likelihood of cross-reactivity to alternative NMBDs in a patient who has previously had an anaphylactic reaction?

The incidence of anaphylaxis for individual NMBDs is unknown due to difficulties establishing accurate values for the numerator (cases) and the denominator (exposures). In the previous two decades, it has been argued that NMBD anaphylaxis has been both over-diagnosed[2] and under-diagnosed.[3] It has also been argued that rocuronium is a drug with either a higher or comparable relative rate of anaphylaxis than its intermediate-duration alternatives.[4–6]

We have estimated the incidence of NMBD anaphylaxis by analysing patients diagnosed with NMBD anaphylaxis over a 10 yr period at the sole referral centre for investigation of intraoperative anaphylaxis in Western Australia. When NMBD sales data are extrapolated across this time period, the sample represents over 1 million patient-exposures.

Intraoperative anaphylaxis should be subsequently investigated to confirm the identity of the triggering agent. As patients with NMBD anaphylaxis frequently cross-react with other NMBDs, and this is not predictable on the basis of structure, skin testing to identify agents that are less likely to cause anaphylaxis on subsequent exposure is required.

Methods

The Western Australian Anaesthetic Drug Reaction Clinic is a specialized diagnostic centre that investigates hypersensitivity in a standardized manner, as recommended by Mertes and colleagues.[3] Ethics approval for publication of this research was granted by the Sir Charles Gairdner Hospital Human

Research Ethics Committee (approval reference QI2728). Patients referred to the clinic for investigation after a clinical event typical of a severe, immediate-type hypersensitivity reaction underwent skin testing to the NMBD administered and all other possible triggering agents. Skin testing followed the intradermal testing protocol outlined by Fisher and Bowey.[7]

Performance and interpretation of the tests was standardized. Intradermal testing was conducted for the aminosteroid agents with a 1:1000 dilution of rocuronium (10 mg ml^{-1}), vecuronium (4 mg ml^{-1}), or pancuronium (2 mg ml^{-1}). The benzylisoquinoliniums were tested at a dilution of 1:10 000 for atracurium (10 mg ml^{-1}) or 1:1000 for cisatracurium (2 mg ml^{-1}). Succinylcholine (50 mg ml^{-1}) was diluted to 1:1000. A volume of 0.02 ml was injected in the volar forearm to produce a 4 mm intradermal bleb and a positive response was achieved if the wheal increased to 8 mm or greater at 20 min. Normal saline was used for the negative intradermal control and a skin prick of morphine 10 mg ml^{-1} or histamine 8 mg ml^{-1} for the positive control to exclude anergy.

Patients were diagnosed with NMBD anaphylaxis only if they fulfilled all of the following criteria. First, there must have been a plausible time relation between NMBD administration and anaphylaxis. Secondly, they must have had a positive intradermal response to the NMBD administered clinically. Thirdly, they must have had negative skin test results for all other potential triggering agents preceding the episode of anaphylaxis. Appropriate skin responses to a positive (histamine SPT) and negative (saline IDT) control were also required for interpretation of skin tests.

Cross-reactivity testing was conducted for patients diagnosed with NMBD anaphylaxis, by intradermal testing or skin prick testing to all other available NMBDs with the exception of mivacurium.

The severity of intraoperative anaphylaxis was graded according to the four-level scale introduced by Mertes and colleagues.[4] Grade 1 intraoperative anaphylaxis consisted of cutaneous signs only. Grade 2 required the presence of measurable but not life-threatening symptoms including a decrease in arterial pressure by more than 30% in association with unexpected tachycardia and cutaneous signs, cough, or difficulty in mechanical ventilation. Grade 3 required the presence of life-threatening reactions, including cardiovascular collapse, while grade 4 describes circulatory inefficacy or cardiac arrest. The severity of reactions was compared between the three most commonly implicated NMBDs by the Freeman–Halton extension of the Fisher exact probability test for a three-by-three contingency table.

The number of patients exposed to NMBDs over the 10 yr period was extrapolated from 5 yr of NMBD ampoule sales data for Western Australia 2007 to 2011, inclusive. These data were purchased from IMS Health (St Leonards, NSW, Australia), using departmental research funds. We estimated the minimum number of ampoules required to administer an ED_{95} dose to a hypothetical 70 kg patient, assumed no ampoule splitting or wastage, and calculated the largest possible number of patients exposed, given the number of ampoules sold. A rate of NMBD anaphylaxis for each NMBD was then calculated, with 95% confidence intervals (CIs) according to a Poisson distribution. Rates were compared by a one-tailed test of Poisson-distributed counts.

Results

Over the 10 yr period from January 1, 2002, to December 31, 2011, 80 patients were diagnosed with life-threatening anaphylaxis to an NMBD; 81% of patients were female, with a mean age of 45 yr (SD 18 yr) and a range from 5 to 91 yr old. Fifty-six per cent of these reactions were triggered by rocuronium (45/80), 21% by succinylcholine (17/80), 11% by vecuronium (9/80), 9% by atracurium (7/80), and 3% by mivacurium (2/80). There were no reported events triggered by pancuronium or cisatracurium.

Eleven patients (14%) suffered grade 4 intraoperative anaphylaxis to an NMBD, and 10 of these received external cardiac compressions. Fifty-five (68%) had a grade 3 reaction, and 14 (18%) had a grade 2 reaction. No patient was diagnosed with IgE-mediated NMBD anaphylaxis after a grade 1 reaction. There was no difference in the severity of reactions for the three most frequently implicated agents ($P=0.33$). Surgery was abandoned in 60% of cases and the patient was admitted to an intensive care unit in 57%.

The annual sales of the seven NMBDs was provided for each ampoule size, and the total dose of each NMBD sold each year is summarized in Figure 1. A total of 1.03 million exposures of NMBD were administered in Western Australia from 2007 to 2011, inclusive, although the high rate of wastage of succinylcholine ampoules is likely to result in over-estimation of exposure. Excluding succinylcholine, there were 578 000 exposures to NMBDs (the 'intermediate-duration NMBDs') over the 5 yr period, or ~1.16 million exposures over the 10 yr period for which the anaphylaxis cases were diagnosed.

Rocuronium had the highest rate of anaphylaxis, at 8.0 episodes per 100 000 administrations over the 10 yr period (95% CI 5.8–11/100 000; see Fig. 2). This was greater than the rate of vecuronium anaphylaxis at 2.8 per 100 000 administrations (95% CI 1.3–5.3/100 000). This difference was statistically significant when considered over the 10 yr period ($P=0.0013$), or when limited to the 5 yr for which sales data are available (9.2 *vs* 3.1/100 000; $P=0.01$). The next most frequently administered NMBD, atracurium, had a rate of 4.01 per 100 000 (95% CI 1.6–8.3/100 000). No cases of pancuronium or cisatracurium anaphylaxis were diagnosed. However, the small number of patients exposed to each of these drugs reduces the precision of this result, and the upper limit of the 95% CIs for rates of anaphylaxis is 33/100 000 and 17/100 000, respectively. Owing to the fact that succinylcholine is frequently drawn up as an emergency drug, and usually discarded rather than administered, a rate of anaphylaxis to succinylcholine could not be determined.