

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-diagnosed² 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 ED₉₅ 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.

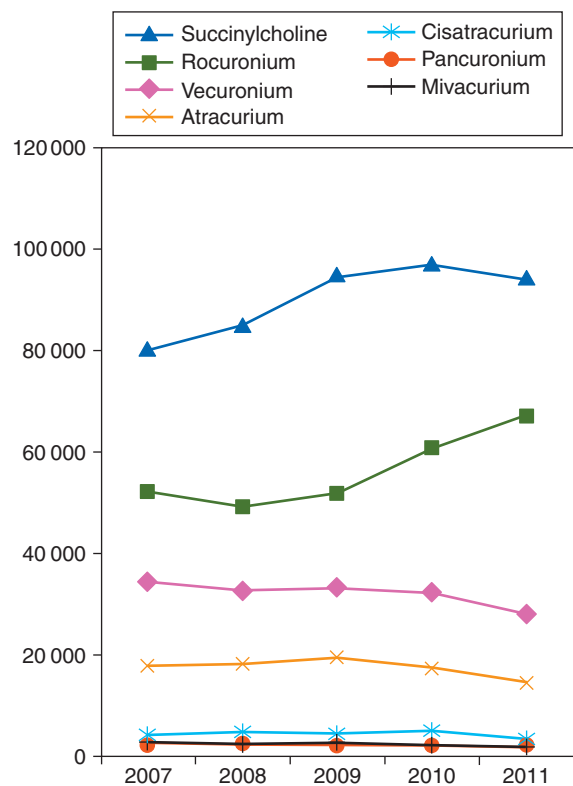


Fig 1 Market share of NMBDs sold annually in Western Australia 2007–2011. Units are number of ED₉₅ doses for a hypothetical 70 kg patient sold.

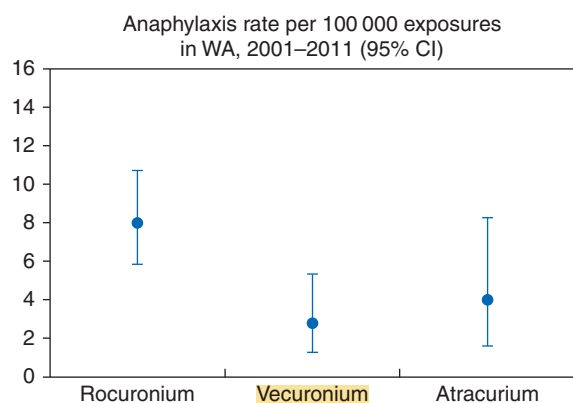


Fig 2 Point estimate of anaphylaxis rate per 100 000 exposures, with 95% CIs.

Of the intermediate-duration NMBDs, rocuronium caused 71% of cases of anaphylaxis over the 10 yr period but had only a 49% share of the intermediate-duration market over the 5 yr period for which data are available. Vecuronium caused only 14% of anaphylaxis, despite a 28% market

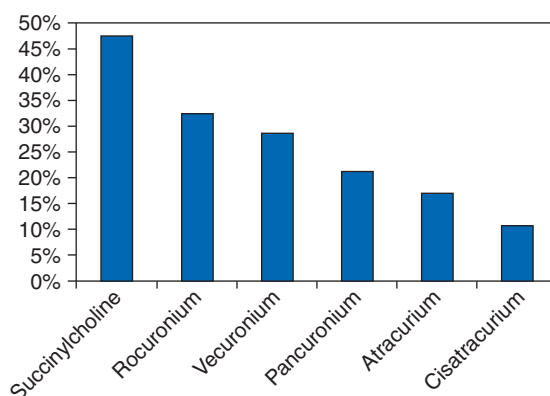


Fig 3 Percentage of cross-reactivity to individual NMBDs. Note that 56% of patients were diagnosed with rocuronium anaphylaxis.

share. Atracurium caused 11% of anaphylaxis with 15% of the market share.

Cross-reactivity results are presented in Figure 3. Of the 45 patients diagnosed with rocuronium anaphylaxis, four were not tested with cisatracurium, three were not tested with pancuronium, and one was not tested with atracurium. Of the seven patients diagnosed with atracurium anaphylaxis, one patient was not tested with vecuronium. Patients diagnosed with NMBD anaphylaxis most frequently cross-reacted with succinylcholine (30 out of 63 patients tested for cross-reactivity). This was followed by rocuronium (11 out of 34 patients tested), vecuronium (20 out of 70 patients tested), and pancuronium (16 out of 76 patients tested). Benzylisoquinoliniums cross-reacted less frequently.

As there is potential for selection bias due to different rates of NMBD usage, cross-reactivity results are presented also according to the agent responsible for referral to the clinic, a clinically useful distinction. Cross-reactivity in patients with rocuronium, succinylcholine, vecuronium, and atracurium anaphylaxis are presented in Figure 4; there were insufficient patients for analysis of the other agents. Patients with rocuronium anaphylaxis were most likely to also skin test positive to succinylcholine (44%) and vecuronium (40%), while pancuronium and atracurium were also frequent cross-reactors (19% and 20%, respectively). Cisatracurium was the least likely to cross-react, at 5%. Patients with succinylcholine anaphylaxis were less likely to cross-react with the other NMBDs, while patients with vecuronium anaphylaxis had a very high rate of cross-reactivity, particularly with other aminosteroid NMBDs, although the sample size is small. None of the seven patients with a diagnosis of atracurium anaphylaxis cross-reacted with the aminosteroid NMBDs.

Discussion

The rate of anaphylaxis to rocuronium in Western Australia was more than twice that of vecuronium. Life-threatening,

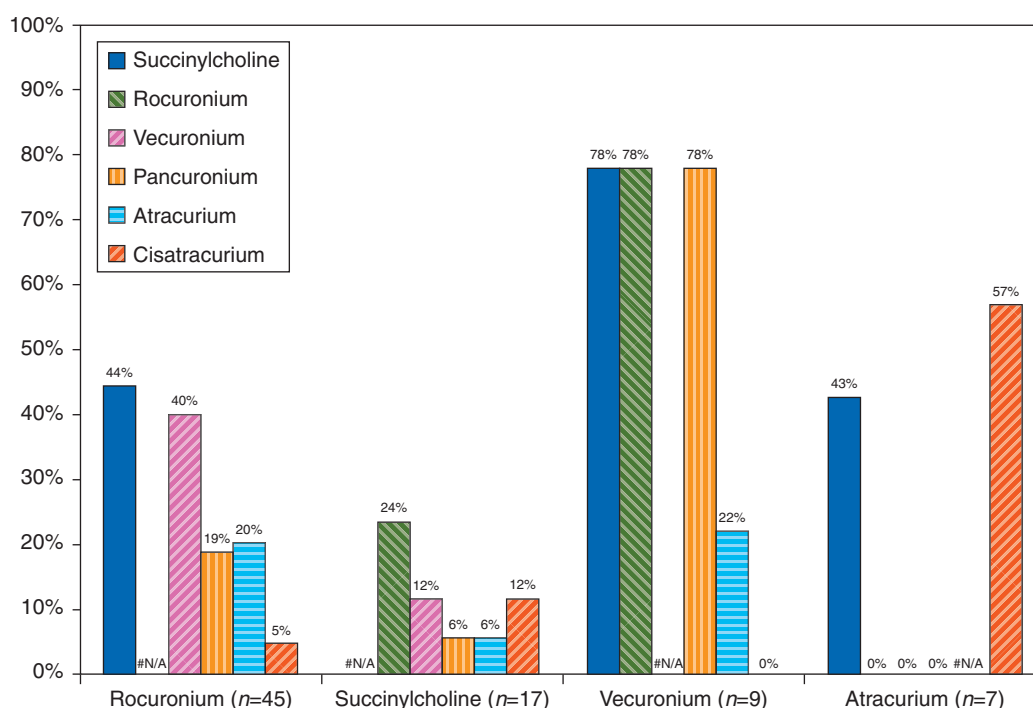


Fig 4 Rates of cross-reactivity for patients diagnosed with anaphylaxis according to the triggering NMDB.

IgE-mediated rocuronium anaphylaxis in Western Australia occurred at a rate of at least 8.0 episodes per 100 000 administrations (95% CI 5.8–11) compared with 2.8 episodes per 100 000 administrations for vecuronium (95% CI 1.3–5.3). This result was statistically significant ($P=0.0013$). Rocuronium was responsible for 56% of cases of NMDB anaphylaxis, while vecuronium only contributed 11%. If one considers only the data for intermediate-duration agents, the excessive burden of rocuronium anaphylaxis becomes even more apparent. Rocuronium was responsible for 71% of these cases of NMDB anaphylaxis, despite only a 49% share of the intermediate-duration market (ratio of 1.5), while vecuronium caused 14% of cases, despite a 28% market share (ratio of 0.50).

NMBD anaphylaxis is a feared complication but one that is difficult to study. This is in part due to the fact that it has a low incidence (1 in 6000–20 000 administrations of NMDB)¹ and a prevalence that varies according to geographical location.⁹ Observed differences have been blamed on under-reporting of adverse drug reactions,^{10 11} non-standardized diagnostic criteria for anaphylaxis,² differences in NMDB-prescribing practices,^{4 12} and variation in the rates of immune sensitization due, at least in part, to differences in community pholcodine exposure.^{8 10 13} Finally, a paucity of accurate and independent NMDB population exposure data has hampered attempts to compare the rates of anaphylaxis of different NMDBs within or between populations.

Errors in the numerator due to under-reporting of cases have been minimized due to several characteristics of our

clinic. Eighty-eight per cent of the population of Western Australia live within 2 h commute of the clinic, which is the only centre in the state that investigates intraoperative adverse drug reactions, and is commercially independent. Anaesthetists share a culture of reporting life-threatening incidents for further investigation as this is considered a standard of care, and failure to report would be apparent to those who cared for the patient in the future. Simultaneous administration of multiple potential triggers and an inability to predict the responsible agent without subsequent skin testing is also likely to minimize non-referral. Although no patients were diagnosed with grade 1 intraoperative anaphylaxis to NMDBs, the majority of patients referred to the clinic after a suspected intraoperative drug reaction had suffered non-life-threatening reactions. This indicates that there is little barrier to referral to our service. Even if under-reporting were to have occurred, our methods could only underestimate the true magnitude of the problem.

Previous attempts to measure the denominator (NMDB exposure) for estimating the incidence of NMDB anaphylaxis have often used data provided directly by pharmaceutical companies.^{6 14} We purchased NMDB sales data from IMS Health—an independent, healthcare information company. Sales data are representative of patient exposures for all agents except succinylcholine, which is frequently drawn up in readiness for unexpected use and usually discarded. Sales data, once corrected for ampoule size, are likely to give a good estimation of the relative exposure to each agent for comparison. The absolute exposure is likely to be

over-estimated (either due to ampoule wastage or administration of more than an ED₉₅ dose), and again this would result in a measurement of the rate of anaphylaxis that is less than the true rate. However, this would influence the estimates for both rocuronium and vecuronium equally, and again any difference measured remains valid.

Sales data were only available for the 5 yr interval 2007–2011 (inclusive). We extrapolated this over the 10 yr that NMBD anaphylaxis data were available. Sales data over the 5 yr period show a trend of increasing rocuronium and diminishing vecuronium sales. We believe that the market trend in the previous 5 yr is likely to have similarly shown an increase in rocuronium market share at the expense of vecuronium as concerns regarding rocuronium anaphylaxis were allayed. The extrapolation of sales data is therefore likely to over-estimate the total rocuronium exposure and under-estimate the total vecuronium exposure. The true difference in NMBD anaphylaxis between agents was therefore likely to be greater than measured. Even if we limit ourselves to the 5 yr that both anaphylaxis and sales data exist, there was a statistically significant difference in the rates of anaphylaxis to rocuronium and vecuronium.

Referral bias is a possible cause of differences in the measured rate of anaphylaxis. The **Weber effect**—the observation that **clinicians are more vigilant and likely to report adverse drug associations in the second year after a drug's approval**—was considered a possible explanation for the high rate of rocuronium anaphylaxis noted in Norway from 1997 to 1999.¹² However, rocuronium was introduced to the Australian market in 1996, and this is unlikely to be a contributing factor during our periods of observation. As the identity of the trigger is often unknown at the time of referral, and attitudes regarding the risk of anaphylaxis to rocuronium do not seem to differ greatly from that of vecuronium (as evidenced by their relative market shares), referral bias is unlikely to be a major contributing factor.

Our findings are consistent with the published international literature. Over a 2.5 yr period in Norway from 1997, the rate of anaphylactic or anaphylactoid reactions to rocuronium was estimated to be 19 (95% CI 13–28) per 100 000 patient exposures, compared with only 4.6 (95% CI 2–17) for vecuronium.¹⁵ In the 2 yr period in **France from January 1999, rocuronium was responsible for 56% of cases anaphylaxis**, despite only a 9.5% share of the intermediate-duration NMBD market, compared with vecuronium with 11%, despite a 12% market share.⁴ In New South Wales in 1999, rocuronium was responsible for more than three-quarters of the cases of anaphylaxis in their sample.⁶

Unfortunately, the identification of rocuronium as an agent with a high risk of anaphylaxis created controversy. The decision by the Norwegian Medicines Agency (NMA) to restrict rocuronium to special indication only, in the year 2000, was criticized for being based on data drawn from a population that was too small, of a condition prone to under-diagnosis and distorted by reporting bias.^{15 16} However, this did not stop other authors using smaller samples to argue that there was no cause for concern regarding the relative

risk of anaphylaxis to rocuronium.^{6 14} Subsequently, a Norwegian expert review found that there was insufficient evidence to support the previous recommendations of the NMA.³

Another limitation of published literature concerned with NMBD anaphylaxis is the reliance on data provided by pharmaceutical companies for estimation of exposure. The rapid increase in the rate of rocuronium anaphylaxis in New South Wales from 1996 to 1999 was assumed to be a result of increased market share.⁶ Drug usage data were provided by the drug manufacturer, which showed a linear increase in total market share from between 20% and 30% in 1996 to between 70% and 80% in 1999. These data differ greatly from published data from France (10% market share in 1997–8,⁵ 8.8% market share in 1999–2000),⁴ the Royal Adelaide Hospital (43% of ampoules ordered in 2000),¹⁷ Norway (market share <50% in 1999),¹⁶ and even its largest market, the USA (market share 54% of intermediate-duration NMBA ampoules sold in 1999).¹² The rocuronium manufacturer also provided 'normalized' market-share data for 1996–9 in the UK to allow Watkins¹⁴ to conclude in 2001 that the rate of rocuronium anaphylaxis was similar to that of vecuronium and atracurium.

Other papers that have discounted any increased risk of anaphylaxis with rocuronium may not be generalizable or relevant to the Australian experience. In 2005, Bhananker and colleagues¹² presented an analysis of Federal Drug Administration reporting of adverse events via the voluntary, MedWatch report program. Ignoring the limitations of a voluntary reporting study,¹⁸ it is notable that more cases of **NMBD anaphylaxis were reported to the FDA from areas outside of the USA than within**. Other studies within the USA have similarly reported a low prevalence of NMBA anaphylaxis,¹⁹ leading some to question the existence of NMBD anaphylaxis as an entity.²

A plausible explanation for the **geographical variation** is **community exposure to the morphine analogue, pholcodine**. A **high rate of exposure** of the **Norwegian** population to pholcodine, before its withdrawal in 2007, is hypothesized to explain the **10-fold difference in the frequency of NMBD anaphylaxis in this country vs Sweden**, where it was not available. Pholcodine has been demonstrated to be a **potent IgE-sensitizing agent**, sensitizing individuals to **epitopes common to NMBDs**. Withdrawal of pholcodine from Norway in 2007 was also correlated with a decrease in community sensitization to these epitopes.¹⁰ This may also explain the **observed difference in the frequency of NMBD anaphylaxis in the USA vs Australia or France**. Pholcodine has been freely available in Australia during the study period (average national consumption 500 kg yr⁻¹ between 2004 and 2008, inclusive), while it was not available in the USA.²⁰ The **UK** and **France** also have **high rates of consumption of pholcodine**, suggesting that our results may be more generalizable to these populations than the USA.

Cross-reactivity data have also been used previously in the literature to estimate the relative risk of anaphylaxis to each individual NMBD in NMBD-allergic patients.⁶ We have presented cross-reactivity data in two ways to allow comparison with other studies, and also to minimize selection bias.

Rose and Fisher⁶ presented the prevalence of cross-reactivity in their NMBD-anaphylaxis series according to each agent tested for cross-reactivity. Their analysis suggested that rocuronium had an intermediate risk of anaphylaxis as the rate of cross-reactivity was less than that of succinylcholine but greater than that of vecuronium. In our series, succinylcholine was again the most common agent to cross-react (Fig. 3). This is consistent with the hypothesis that succinylcholine has a high rate of anaphylaxis due to its ability to bind to IgE with less specificity and cross-link FcεR-bound IgE due to its flexible structure and accommodating paratope.²¹ Rocuronium was the next most frequent cross-reactor. Pancuronium (noted to have an inflexible structure) and other aminosteroids were less likely to cross-react with the NMBD responsible for the clinical episode of anaphylaxis. These results may be interpreted as suggesting that succinylcholine has the highest risk of anaphylaxis, rocuronium has a higher risk than vecuronium, and that cisatracurium is the least likely NMBD to cause anaphylaxis. Both studies are subject to selection bias as the high rate of the use of rocuronium (and high incidence of anaphylaxis to rocuronium) will select patients to the sample that are rocuronium-hypersensitive. If the pattern of cross-reactivity is non-random, for example, if there is increased cross-reactivity between aminosteroid NMBDs, then this will cause confounding. For this reason, we believe that this analysis should be interpreted with caution when estimating the population risk of anaphylaxis to individual agents.

To determine the agent with the least likelihood of precipitating anaphylaxis on re-exposure to an NMBD after previous NMBD anaphylaxis, skin testing to alternative agents is routinely completed. There were enough patients diagnosed with anaphylaxis to rocuronium, succinylcholine, vecuronium, and atracurium to analyse the patterns of cross-reactivity separately. Interestingly, it appears that the pattern varies according to which agent was responsible for the primary anaphylactic event (Figure 4). For example, patients selected by an episode of anaphylaxis to succinylcholine infrequently cross-reacted with other agents. On the other hand, patients who had suffered anaphylaxis to vecuronium frequently reacted to the other aminosteroid agents, and succinylcholine. After atracurium anaphylaxis, patients frequently reacted with cisatracurium and succinylcholine but rarely with the aminosteroids. These results are consistent with the hypothesis that succinylcholine has a structure that is able to accommodate a wide range of IgE-binding sites, whereas vecuronium demands more specific binding. Of course, no NMBD is risk-free in this population, and all should be avoided if possible. However, if an NMBD must be administered to a patient and cisatracurium, among others, tests negative then this may be the safest choice in a patient suspected of anaphylaxis to rocuronium or vecuronium.

In summary, anaphylaxis to NMBDs is a significant clinical problem. Rocuronium causes IgE-mediated anaphylaxis at an increased rate compared with vecuronium. This

characteristic of rocuronium has been suggested previously, and yet frequently dismissed. Although there are many factors that influence the choice of NMBD, clinicians should be aware of the likely increased anaphylaxis risk of rocuronium when considering the need for an intermediate-duration NMBD.

Declaration of interest

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