

A review of 19 years of anaphylaxis cross-reactivity data to muscle relaxants in New Zealand

Zyllan P Spilsbury, Han Truong

Anaphylaxis is “a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy causing substance”.¹ A complex immunological response (usually involving immunoglobulin E [IgE] antibodies) results in the secretion of multiple, biologically active products that cause characteristic multisystem signs and symptoms.² Anaphylaxis remains a major cause of anaesthesia attributable death, with a reported mortality rate between 1% and 3.5%.³⁻⁵

The incidence of anaesthesia associated anaphylaxis varies between countries (1:1,250 to 1:13,000).⁶ The National Audit Project data (UK) reports that neuromuscular blocking agents (NMBAs) are used in approximately 50% of anaesthetics and are the second most common trigger agent for anaphylaxis associated with anaesthesia after antibiotics.⁴

The quaternary ammonium epitope has a recurring presence throughout the different NMBA classes (suxamethonium, steroid and benzylisoquinolinium). This similarity predisposes NMBAs to significant cross-reactivity between the classes.

Our aim is to estimate the rates of cross-reactivity between the different NMBAs.

Method

This is a minimal risk observational study and therefore did not require ethical approval. These data include consecutive patients with intradermal tests (IDT) data sent to New Zealand's Centre for Adverse Reactions Monitoring (CARM) retrospective database for collation between February 2000 and June 2019. All the patients were diagnosed with NMBA anaphylaxis because of a suggestive clinical event and followed-up by an allergy testing service who adhere to the Australian and New Zealand Anaesthetic Allergy Group (ANZAAG) allergy testing guidelines. The referral data includes demographics, a clinically

suspected trigger NMBA (as the trigger for anaphylaxis) and the positive results of IDT. We included all patients who received IDT for a NMBA panel, including a combination of steroid NMBAs (rocuronium, vecuronium, pancuronium), benzylisoquinolinium NMBAs (mivacurium and atracurium) and suxamethonium during their follow-up. A Fisher's exact test was used to test for an association between the trigger NMBA and cross-reactivity (positive for the trigger and at least one other agent).

Results

Five hundred and one patients were referred to the CARM database between 2000 and 2019 with a confirmed diagnosis of NMBA anaphylaxis. Forty-four patients were excluded for incomplete IDT data. Three patients were excluded because the NMBA is no longer relevant to modern practice (gallamine or alcuronium).

The number of patients included for cross-reactivity analysis was 454. The population included 343 female and 111 male patients. The median (IQR) age was 52 (37–64) years.

Of the 454 patients diagnosed with NMBA anaphylaxis, the number of events for each trigger NMBA was rocuronium (n=242), suxamethonium (n=143), atracurium (n=42), mivacurium (n=7), pancuronium (n=3) and vecuronium (n=17). One hundred and ninety-six patients (43.2%) demonstrated no cross-reactivity beyond the trigger NMBA. Thirty-two patients had a negative IDT for the trigger NMBA despite a clinical diagnosis of NMBA anaphylaxis, including: suxamethonium (n=9), rocuronium (n=17), atracurium (n=4), mivacurium (n=2). Twenty-five patients had negative cross-reactivity patterns, including being negative for the trigger NMBA.

There is a statistically significant association between the trigger agent and cross-reactivity (testing positive for the trigger and at least one other agent), $p < .0001$. Those with suxamethonium

Table 1: The positive intradermal cross-sensitivity testing results.

Index NMBA	(Events)	Negative skin test for index agent	No cross-reactivity	Cross reactivity; n(%)					
				Suxamethonium	Rocuronium	Atracurium	Vecuronium	Mivacurium	Pancuronium
Suxamethonium	143	9 (6.29)	94 (65.73)	134 (93.71%)	27 (18.88)	9 (6.29)	10 (6.99)	10 (6.99)	6 (4.20)
Rocuronium	242	17 (7.02)	79 (32.64)	107 (44.21%)	225 (92.98)	15 (6.20)	68 (28.10)	10 (4.13)	49 (20.25)
Atracurium	42	4 (9.52)	18 (42.86)	7 (16.67%)	9 (21.43)	38 (90.48)	2 (4.76)	17 (40.48)	0 (0)
Vecuronium	17	0 (0)	3 (17.65)	5 (29.41)	7 (41.18)	3 (17.65)	17 (100)	4 (23.53)	8 (47.06)
Mivacurium	7	2 (28.57)	1 (14.29)	1 (14.29%)	1 (14.29)	5 (71.43)	1 (14.29)	5 (71.43)	1 (14.29)
Pancuronium	3	0 (0)	1 (33.33)	1 (33.3%)	1 (33.33)	0 (0)	0 (0)	1 (33.33)	3 (100)
Total	454	32	196	255	270	70	98	47	67

Figure 1: Rates of cross-reactivity for patients diagnosed with anaphylaxis according to triggering NMBA.

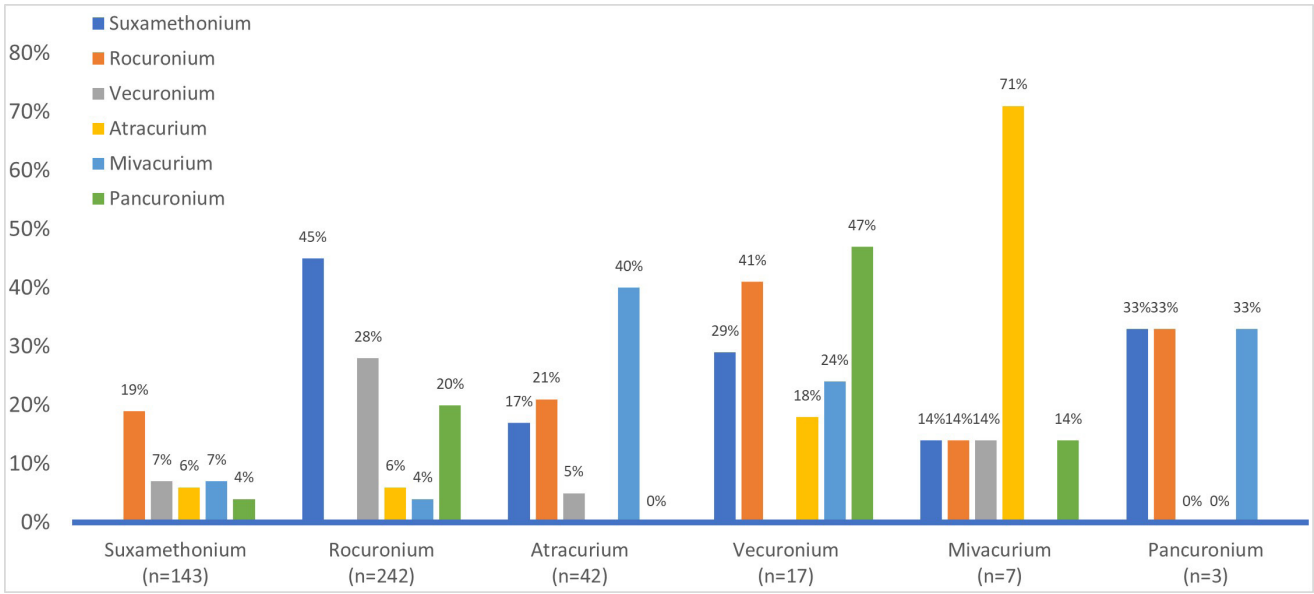
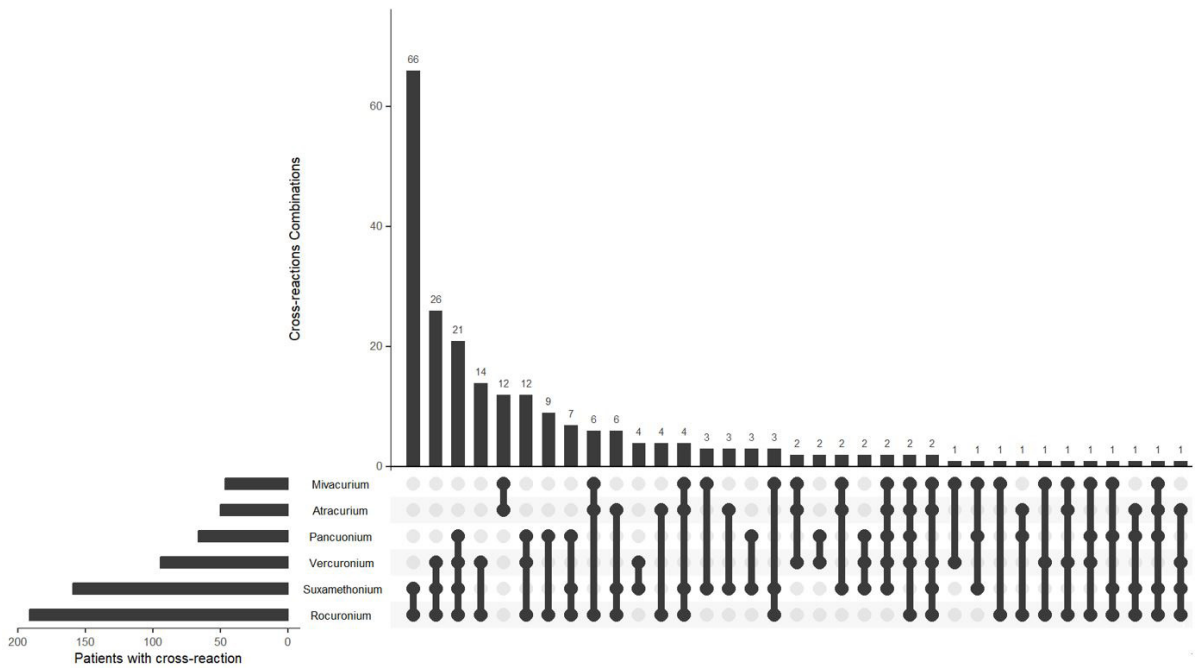


Figure 2: The common patterns of cross-reactivity seen on IDTs for NMBAs.



as the trigger NMBA were significantly less likely to have cross-reactivity than those with rocuronium or vecuronium as the trigger agent ($p < .05$).

The cumulative number of positive IDT reactions for each NMBA was rocuronium ($n=270$), suxamethonium ($n=255$), vecuronium ($n=98$), atracurium ($n=70$), pancuronium ($n=67$) and mivacurium ($n=47$).

Discussion

These data are in keeping with the current evidence which suggests that suxamethonium and rocuronium are high-risk for isolated and cross-reactive anaphylaxis because one or both were positive on IDT in 85% (386/454) of patients in this population.⁷⁻⁹ Atracurium and mivacurium demonstrate high cross-reactivity, in keeping with their similar benzyliisoquinolinium structure.

Vecuronium as a trigger NMBA had the highest percentage cross-reactivity with other steroid NMBAs (88.2%) compared to rocuronium (48.8%) and pancuronium (33.3%). Although the total number of presentations as the trigger NMBA are low, vecuronium consistently appears to be more likely to cross react with other steroid NMBAs.⁸ It is possible that the mono-quaternary ammonium epitope and adjoining structures found on vecuronium act to sensitise IgE antibodies to a broad spectrum of molecules.

National estimates of usage for each NMBA to inform a true denominator for risk of anaphylaxis are unavailable. Our cross-reactivity data suggest a lower rate of cross-reactivity of atracurium compared with suxamethonium and rocuronium, which is in keeping with Reddy et al., who report a lower anaphylaxis rate and a higher exposure

rate to atracurium compared to other NMBAs.⁷

The voluntary referral bias to the CARM database limits the data's accuracy as a numerator for anaphylaxis risk to NMDA. The database may be subject to referral bias because patients are referred to CARM without accompanying clinical notes to validate the diagnosis.

Predicting cross-reactivity based on trigger NMBA or class of NMBA is not a reliable way to inform NMBA selection in patients who have previously experienced anaphylaxis under anaesthesia. Any cases of suspected anaphylaxis under general anaesthesia should be referred for specialised allergy testing. ANZAAG provides an evidence-based approach to this process with guidelines for the follow-up and testing of suspected cases of anaesthesia associated anaphylaxis.¹⁰

Once an allergy to a NMBA is confirmed, it is often recommended that all NMBAs should be avoided in future due to some uncertainty with interpreting IDT results and variability in cross-sensitivity patterns. However, increasing experience with basophil activation tests and direct awake intravenous provocation testing of NMBA may soon enable the safe recommendation of a specific NMBA to use in patients that have experienced previous NMBA anaphylaxis.^{8,11}

If NMBAs cannot be avoided following an anaphylaxis event, atracurium shows positive IDT results in only 15% (70/454) of the study population and therefore could be considered the most appropriate first line NMBA. Caution should be maintained for class effect cross-reactivity in the benzyliisoquinolinium group. The risk of inducing anaphylaxis with NMBAs should be a consideration for all physicians caring for patients under general anaesthetic.

COMPETING INTERESTS

Nil.

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