16 Neuromuscular blocking agents and reversal agents

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Key findings

- In the baseline survey, neuromuscular blocking agents (NMBAs) were the drugs anaesthetists most commonly suspected to be triggers of anaphylactic reaction and were the drugs most commonly avoided because of risk of anaphylaxis.

- Sixty-four cases of Grade 3–5 NMBA-induced anaphylaxis were confirmed by the review panel – 33% of all cases.

- In contrast to the majority of previously published studies, NMBAs were the second most common trigger agent, being 1.4-fold less common than antibiotic-induced anaphylaxis.

- Suxamethonium was almost twice as likely to cause anaphylaxis as any other NMBA, with a rate of 11.1 per 100,000 administrations.

- The main non-depolarising NMBAs all have very similar incidences of anaphylaxis, meaning that anaphylaxis risk should not be a major reason for choosing between them.

- Anaesthetists suspected NMBAs to be the cause of anaphylaxis 20–40% more often than was the case. This was most pronounced with atracurium.

- In 10% of cases of atracurium-induced anaphylaxis, the mechanism was non-allergic.

- Sugammadex was used during resuscitation of several cases of rocuronium-induced anaphylaxis and in half of these cases no further resuscitation drugs were needed, but it is difficult to draw strong conclusions.

- Sugammadex was also used for management of non-rocuronium-induced anaphylaxis, with no clear evidence of benefit.

- A single case of sugammadex-induced anaphylaxis was identified by the review panel.

- There were no reported cases of anaphylaxis due to neostigmine.

- Allergy Clinic investigation of NMBA-induced anaphylaxis had significant shortcomings. Use of the NAP6 minimum NMBA panel will help identify the culprit and safe alternatives, especially for rapid-sequence induction.

What we already know

Neuromuscular blocking agents (NMBAs) are generally accepted to be responsible for a high proportion of cases of perioperative anaphylaxis. Major centres report that NMBAs are responsible for between 40% and 66% of all cases (Leysen 2013, Mertes 2003, Mertes 2011), but the proportion appears to be historically lower in Denmark (Garvey 2001) and, until recently, higher in Norway (Harboe 2005).

Sensitisation to NMBAs may result from previous exposure, but this is not always the case: it is likely that environmental exposure to the quaternary ammonium (QA) epitope is sufficient in some individuals to stimulate allergy to NMBAs (Didier 1987). In addition to QA compounds found in detergents and many other products, there is evidence that exposure to pholcodine-containing cough medicines may cause sensitisation to NMBAs (Johansson 2010): NMBA anaphylaxis has declined in Norway since withdrawal of cough medicine containing pholcodine (de Pater 2017).

The quaternary ammonium epitope present in all NMBAs is predominantly responsible for their allergenic properties. Currently-used NMBAs are either monoquaternary (vecuronium and rocuronium) or bisquaternary (suxamethonium, atracurium, mivacurium, pancuronium). There is no evidence that the risk of anaphylaxis is related to the number of quaternary ammonium groups. Individuals may be allergic to more than one NMBA. Cross-sensitivity, based on skin testing and specific IgE, is common, with suxamethonium being the most commonly cross-reacting drug (Sadleir 2013). Cross-sensitivity may occur between different classes of NMBA (for example, benzylisoquinoline and aminosteroid) as well as within classes. Therefore if an NMBA is suspected as a cause of anaphylaxis, it is important that a panel of NMBAs is tested in the allergy clinic to detect cross-reactivity and to establish safe alternative NMBAs (Ewan 2010), especially for use during rapid sequence induction (RSI). In Chapter 13, we proposed the NAP6 NMBA minimum panel – the minimum panel of NMBA tests, which is judged sufficient if it includes the suspected agent, together with suxamethonium, rocuronium, and either atracurium or cisatracurium (Egner 2017).

Non-allergic anaphylaxis may occur with atracurium and mivacurium. There is recent evidence implicating specific receptors on the surface of mast cells (McNeil 2014). Variation in receptor expression may explain why these drugs cause non-IgE-mediated mediator release in some individuals but not in others.

No previous study has undertaken concomitant studies of prevalence of NMBA events and NMBA exposure, enabling incidence to be estimated directly; NAP6 collected information on the number of patients receiving NMBAs during the same year

as the case reporting phase. Previous studies have relied on sales of drug ampoules to estimate the number of patients receiving individual drugs. Ampoule sales are unlikely to accurately reflect the number of patients being exposed. This is particularly important in the case of suxamethonium where ampoule sales are likely to exceed actual usage as a result of high rates of waste when the drug is prepared 'just in case'. It is generally accepted that, among NMBAs, suxamethonium carries the highest risk of anaphylaxis. It has also been suggested that rocuronium is associated with a relatively higher risk of anaphylaxis compared with vecuronium (Sadleir 2013).

In relation to reversal agents, very few cases of allergic reactions to neostigmine have been reported in the world-wide literature (Seed 2000, Hermite 2015). Sugammadex is a known cause of perioperative anaphylaxis: a recent systematic review identified 15 cases of hypersensitivity to this reversal agent – 11 patients underwent skin testing and 10 were positive (Tsur 2014).

Numerical analysis

Baseline and allergen data

In the baseline survey, NMBAs were the drugs anaesthetists most commonly suspected as the trigger when they suspected anaphylaxis, and were also the drugs anaesthetists most commonly avoided because of concerns about anaphylaxis. Among these, suxamethonium and rocuronium were particularly prominent, with anaesthetists three to four times more likely to avoid these than atracurium (see Chapter 7, Anaesthesia baseline survey).

NMBAs were used in 47.2% of general anaesthetics (approximately 1.2 million patients per year) with atracurium accounting for 49.1% of NMBA uses, rocuronium 40.6% and suxamethonium 11.2%. A reversal agent was used in approximately two thirds of operations where a non-depolarising NMBA was used (≈700,000 cases per year), of which neostigmine was used in 91% and sugammadex in 9% (details in Chapter 9, Allergen Survey).

Numerator data

There were 81 cases in which the anaesthetist suspected life-threatening anaphylaxis to an NMBA (Table 1).

Sixty-four cases of anaphylaxis were triggered by NMBAs, 25% of all cases, 33% of identified culprits and 32% of cases leading to death or cardiac arrest. Ninety-five per cent of NMBA-induced reactions presented within five minutes. Rocuronium was the most commonly identified NMBA (27 cases, 42%), followed by atracurium (23 cases, 35%) and suxamethonium (14 cases, 22%). In one case, suxamethonium and rocuronium were equally 'highly likely' to have been the cause of anaphylaxis, and both drugs are included in the numerator – ie. 65 potential trigger agents but only 64 cases.

There were no cases of anaphylaxis due to vecuronium, pancuronium or cisatracurium. Non-allergic anaphylaxis to atracurium was identified in three cases, and to mivacurium in a single case.

Table 1 shows the NMBAs identified during the registry phase of NAP6 as causative agents, together with their absolute and relative frequency.

The incidences of the three most prevalent NMBAs were:

- *Rocuronium:*
  27/459,047 = 1 in 17,002 (95% CI 1 in 11,686 – 1 in 25,799)
- *Atracurium:*
  23/554,543 = 1 in 24,111 (95% CI 1 in 16,069 – 1 in 38,034)
- *Suxamethonium:*
  14/126,086 = 1 in 9,006 (95% CI 1 in 5,368 – 1 in 16,473).

Fewer anaphylactic episodes were found to be due to NMBAs than was suspected by the reporting anaesthetists. In 71% of cases where the anaesthetist suspected an NMBA, the culprit was confirmed by the review panel, and in 14.3% an alternative culprit was identified. The ratio of suspected/confirmed cases was 1.4 for atracurium, 1.3 for rocuronium and 1.1 for suxamethonium (Table 1).

Table 1. NMBAs confirmed as causative agents by the panel, absolute and relative risk
*Data from the NAP6 Activity/Allergen Survey (see Chapter 9). In one case, suxamethonium and rocuronium were equally 'highly likely' to have been the cause, ie, 64 cases but 65 likely culprits.

	Cases suspected by anaesthetist	Cases confirmed by review panel	Proportion of UK NMBA usage*	Patients receiving the drug per annum*	Anaphylaxis rate/100,000 administrations	Relative risk of anaphylaxis (Atracurium=1)
Atracurium	32	23	49.1%	554,543	4.15	1
Rocuronium	34	27	40.6%	459,047	5.88	1.42
Suxamethonium	16	14	11.2%	126,086	11.1	2.67
Mivacurium	0	1	2.7%	30,786	3.25	0.78
Vecuronium	0	0	2.2%	24,315	–	–
Cisatracurium	0	0	1.6%	18,629	–	–
Pancuronium	0	0	0.6%	7,059	–	–

Risk of anaphylaxis

The estimated rates of life-threatening anaphylaxis per 100,000 patients are atracurium 4.2, rocuronium 5.9, and suxamethonium 11.1 (Table 1). Suxamethonium is almost twice as likely to cause anaphylaxis as any other NMBA. Among the non-depolarising NMBAs the relative risks are all notably similar, with no agent having a risk more than 50% higher or lower than atracurium.

In paediatric practice, NMBA-induced anaphylaxis was less common, probably reflecting lower rates of administration in this patient group. This is discussed further in Chapter 19, Paediatrics.
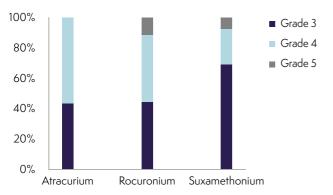
Presenting features and clinical features during NMBA-induced anaphylaxis

These features are discussed in detail in Chapter 10, Clinical features. To summarise – anaphylaxis induced by NMBAs presented rapidly (85% in <5 minutes, 92% in <10 minutes); hypotension was the commonest presenting feature and was particularly prominent in atracurium-induced anaphylaxis, while bronchospasm/raised airway pressure was more common in suxamethonium-induced anaphylaxis.

Severity

Suxamethonium anaphylaxis was more likely to be of severity Grade 3 than NMBA-induced anaphylaxis caused by other agents (Figure 1). Of nine deaths with an identified trigger, four were due to NMBA anaphylaxis; rocuronium was the trigger agent in three cases and suxamethonium in one case.

Figure 1. Severity of NMBA-induced anaphylaxis

Allergy clinic investigation and diagnosis

Rocuronium was identified by the allergy clinics more frequently than atracurium. There was greater diagnostic uncertainty with atracurium than rocuronium, possibly reflecting the former's propensity for non-allergic anaphylaxis in which skin tests are negative and mast cell tryptase levels may be less elevated. In 10% of cases where atracurium was the culprit agent, the review panel identified non-allergic anaphylaxis as the mechanism, and the mechanism was uncertain in an additional 13%. Pancuronium and cisatracurium were not implicated either by the reporters or the review panel.

We judged adequacy of NMBA investigations based on the NAP6 NMBA minimum panel described above. In 113 cases where the review panel judged clinic investigation for NMBA-induced anaphylaxis was necessary, a sufficient NMBA minimum panel was tested in 67%, with two cases being unclear. The clinic did not identify a safe alternative NMBA in six (5%) cases. Skin testing with the suspected agent was not performed in three (3%) cases and suxamethonium was not tested in four (4%) cases. In sixteen (14%) cases the review panel considered that the patient may be at future risk of anaphylaxis as a result of inadequate advice being given to the patient.

Previous exposure to pholcodine was sought in only 15 patients at the allergy clinic and was recorded in only two patients, both of whom had NMBA-induced anaphylaxis (rocuronium and suxamethonium).

Cross-reactivity

An incomplete picture of cross-reactivity was obtained, as one third of patients were not tested with a full panel of NMBAs. In 27 cases of rocuronium-induced anaphylaxis, cross-sensitivity to other NMBAs was identified on skin prick testing in four, of which suxamethonium was the most common, followed by vecuronium and pancuronium. An additional five patients with rocuronium-induced anaphylaxis were cross-sensitive to atracurium on intradermal testing. Cross-sensitivity to two or three NMBAs was common. Of 23 cases of atracurium anaphylaxis, four showed skin prick cross-sensitivity to cisatracurium and three to mivacurium. Five of 14 patients with suxamethonium anaphylaxis showed cross-sensitivity on skin prick testing and a further two on intradermal testing. In these seven cases, cross-sensitivity was equally likely to occur to aminosteroid and benzylisoquinolinium NMBAs, and one was sensitive to all NMBAs. A total of 17 patients showed cross-reactivity – approximately 40% of those where this was explored.

Reversal agents

No episodes were due to neostigmine. Sugammadex was the suspected trigger agent in two cases but was only confirmed in one case. In this case hypotension, urticaria and hypoxaemia developed in the recovery room approximately 15 minutes after administration. Skin prick and intradermal tests were positive at 1:10 dilution and 1:1000 dilution respectively. The Allergen Survey estimated that sugammadex was administered to 14% of patients receiving rocuronium (Chapter 9, Allergen Survey). We have not estimated the numerical incidence of sugammadex-induced anaphylaxis due to the small number of cases. Neither of the two suspected cases of sugammadex-induced-anaphylaxis was reported to MHRA.

Use of sugammadex for treatment during rocuronium-induced anaphylaxis and anaphylaxis induced by other drugs

This is discussed in Chapter 11, Immediate management and departmental organisation.

Discussion

Anaesthetists appeared to have a high index of suspicion that anaphylaxis is likely to be caused by an NMBA, and they suspected that anaphylaxis was caused by an NMBA approximately 40% more often than was actually the case. The ratio of suspected to confirmed cases was highest for atracurium (1.4:1) and lowest for suxamethonium (1.2:1). This is an unexpected finding as suxamethonium is widely known to be the most allergenic NMBA.

Despite suxamethonium being associated with a higher risk of anaphylaxis, its use should be decided on the overall balance of clinical advantages and disadvantages on a case-by-case basis.

Conclusions concerning the relative incidence of atracurium and rocuronium-induced anaphylaxis should be drawn cautiously. The difficulties inherent in interpreting the reported incidences of uncommon anaphylactic events are described by Laake and colleagues (Laake 2001). In particular, marginal under-reporting has a disproportionately large effect on calculated incidence.

In contrast to the many previously published studies (Mertes 2011, Leysen 2013), NMBAs were the not the most common trigger agent overall: antibiotics were identified as the culprit by the review panel 1.4 times more frequently than NMBAs. It is not known whether changes in the prevalence of antibiotic and NMBA sensitisation in the population, the pattern of perioperative antibiotic use, or the choice of NMBA may have contributed to this trend. NMBAs accounted for approximately one third fewer cases of anaphylaxis than antibiotics, but carry at least as high a risk as antibiotics per administration, with the exception of teicoplanin. The lower prevalence of NMBA-induced anaphylaxis observed is due to ≈2.5 million administrations of antibiotics to surgical patients per year compared with ≈1.2 million administrations of NMBAs. The use of NMBAs in the UK does not appear to have declined significantly – 46% of UK patients undergoing general anaesthesia received an NMBA in 2013 (Sury 2014), and 47.2% in 2016 (Chapter 9, Allergen Survey). However, it is probable that the number of patients receiving suxamethonium, the most allergenic NMBA, is declining. In the 2013 NAP5 Activity Survey, suxamethonium was administered to 13.6% of non-obstetric patients receiving an NMBA, falling to 11.2% in 2016 (Chapter 9, Allergen Survey). In the obstetric setting the fall was even more dramatic – from 92% in 2013 to 72.5% in 2016 (Chapter 20, Obstetric anaesthesia).

Establishing the true incidence, ie. risk, is dependent on an accurate estimation of the number of patients exposed to the trigger agent over the study period. Calculation of the incidence of NMBA-induced anaphylaxis has been hampered in the past by difficulty in obtaining accurate denominator data. Reddy *et al* studied concomitant exposure and anaphylaxis rates over a 6-year period during which the pattern of perioperative anaphylaxis may not have been constant (Reddy 2015). Sadleir, in Western Australia (WA), compared incidence over a 10-year period using 5-year ampoule sales by pharmaceutical companies (Sadleir 2013). The incidence per 100,000 administrations was 8.0, 4.0 and 2.8 for rocuronium, atracurium and vecuronium respectively. In the NAP6

study, the incidence of atracurium anaphylaxis was similar to the WA study, but the incidence of rocuronium-induced anaphylaxis was lower. There are several possible reasons why these estimated incidences do not match exactly with NAP6 data. In the WA study the denominator was reliant on ampoule sales which may not accurately reflect the number of patients receiving the drugs: large patients or those undergoing prolonged procedures may require more than one ampoule and, conversely, drugs may be drawn up and not administered or may simply expire and be disposed of. As suxamethonium is frequently drawn up as an emergency stand-by drug, non-administration of opened ampoules is common. For this reason, previous studies have been unable to provide an accurate estimate of the rate of suxamethonium anaphylaxis. It is also possible that the sensitisation rate in the general population through previous NMBA exposure and environmental exposure to similar molecules differs between the UK and WA. In the UK, the number of patients receiving atracurium exceeds that of rocuronium, whereas in WA, rocuronium has three times the market share of atracurium. Vecuronium is used very infrequently in the UK, representing only 2.2% of all NMBA administrations (Chapter 9, Allergen Survey), but its market share in WA is intermediate between atracurium and rocuronium.

Among survivors of perioperative anaphylaxis, severity, as determined by the review panel, was approximately equally divided between Grade 3 and Grade 4 for atracurium and rocuronium, but a greater proportion of suxamethonium-induced anaphylaxis was Grade 3. Sadleir (Sadleir 2013) reported many fewer Grade 4 NMBA reactions than Grade 3. The greater severity of anaphylaxis in the current study may be partially explained by the inclusion of all patients with profound hypotension (systolic blood pressure <50 mmHg) in the Grade 4 category as a part of the methodology (see Chapter 5, Methods).

Four deaths were attributed directly or indirectly to NMBA-induced anaphylaxis, representing 44% of those fatalities with an identified trigger. The review panel considered that one case of anaphylaxis was definitely caused by rocuronium and one definitely by suxamethonium. Rocuronium was probably the trigger in a further two cases. Statistical analysis of these data would not provide meaningful results. Fatalities due to perioperative anaphylaxis are further considered in Chapter 12, Deaths, cardiac arrest and profound hypotension.

Non-allergic anaphylaxis was positively identified by the review panel in four cases, three of which were due to atracurium and one to mivacurium. Non-allergic anaphylaxis tends to be less severe than its allergic counterpart (Low 2016); Grade 1 and Grade 2 hypersensitivity were excluded from NAP6, probably explaining the small number of non-allergic cases in comparison with many studies in which mild hypersensitivity reactions were included.

It is impossible to draw firm conclusions about the prevalence of cross-sensitivity to NMBAs from NAP6 data, but approximately 40% of those tested adequately showed this. Given the infrequent use of a full NMBA testing panel by allergy clinics, NAP6 data should be considered to be minimum estimates. Only if a full NMBA panel is universally adopted can the true prevalence of cross-sensitivity be established.

Pholcodine exposure in cough medicines has been implicated in sensitisation to the quaternary ammonium epitope, especially in relation to rocuronium-induced anaphylaxis. Consumption of pholcodine per million inhabitants is approximately five times greater in Australia than in the UK (Johansson 2010, Sadleir 2013). A minority of allergy clinics (18%) ask patients about their consumption of pholcodine-containing cough medicines (Egner 2017 and Chapter 13 Allergy clinic baseline survey). In NAP6, of 81 cases where NMBA-induced anaphylaxis was suspected by the anaesthetist, information on pholcodine exposure was entered in only 15. Of these, only two patients were recorded as having taken pholcodine-containing cough medicine. Interpretation of these data is not possible and further UK studies are needed to explore any causal relationship.

Recommendations

Institutional

1. Allergy clinics should adhere to published guidelines on the investigation of suspected NMBA anaphylaxis. When NMBA allergy is diagnosed the clinic should identify a safe alternative, including for rapid sequence induction (ie. establishing whether either suxamethonium or rocuronium is safe). The NAP6 NMBA minimum panel is suitable for this.

Individual

2. Except in cases of known or suspected allergy to specific NMBAs, the risk of anaphylaxis should not be an over-riding factor in choice of NMBA, as this varies little between NMBAs.

Research

3. Further research on population sensitisation by pholcodine is needed. If a causal association is confirmed, withdrawal of pholcodine-containing medicines from the UK market should be formally considered.

4. There remains uncertainty about the benefits or potential harm of administering sugammadex during resuscitation of perioperative anaphylaxis and for management of rocuronium-induced anaphylaxis specifically. Clinical trials would provide valuable evidence.

References

Didier 1987: Didier A, Cador D, Bongrand P *et al.* Determinants in Allergy to Muscle Relaxants. J Allergy & Clin Immunol 1987: 79: 578–84.

Egner 2017: Egner W, Cook TM, Harper N *et al.* Specialist Perioperative Allergy Clinic Services in the UK 2016: Results from the Royal College of Anaesthetists 6th National Audit Project. Clin Exp Allergy 2017: 47: 1318–30.

Ewan 2010: Ewan PW, Dugué P, Mirakian R, Dixon TA, Harper JN, Nasser SM. BSACI Guidelines for the Investigation of Suspected Anaphylaxis during General Anaesthesia. Clin Exp Allergy 2010: 40: 15–31.

Garvey 2001: Garvey LH, Roed-Petersen J, Menné T, Husum B. Danish Anaesthesia Allergy Centre - Preliminary Results. Acta Anaesthesiol Scand 2001: 45: 1204–9.

Harboe 2005: Harboe T, Guttormsen AB, Irgens A, Dybendal T, Florvaag E. Anaphylaxis during Anesthesia in Norway. Anesthesiology 2005: 102: 897–903.

Hermite 2015: Hermite L, Louvier N, Hilaire P, Orry D, Seltzer S, Collet E. Neostigmine Induced Anaphylaxis in the Wake of Surgery. Anaesthesia 2015: 34: 109–11.

Johansson 2010: Johansson SGO, Florvaag E, Öman H *et al.* National Pholcodine Consumption and Prevalence of IgE-Sensitization: A Multicentre Study. Allergy 2010: 65: 498–502.

Laake 2001: Laake JH, Rottingen JA. Rocuronium and Anaphylaxis - a Statistical Challenge. Acta Anaesthesiol. Scand. 2001: 45: 1196–1203.

Leysen 2013: Leysen J, De Witte L, Bridts CH, Ebo DG. Anaphylaxis during General Anaesthesia: A 10-Year Survey 1 at the University Hospital of Antwerp. P Belg Roy Acad Med 2013: 2: 88–100.

Low 2016: Low AEJ, McEwan C, Karanam S, North J, Kong KL. Anaesthesia-Associated Hypersensitivity Reactions: Seven Years' Data from a British Bi-Specialty Clinic. Anaesthesia 2016: 71: 76–84.

McNeil 2014: McNeil BD, Pundir P, Meeker S *et al.* Identification of a Mast Cell-Specific Receptor Crucial for Pseudo-Allergic Drug Reactions. Nature 2014: 519: 237–41.

Mertes 2003: Mertes PM, Laxenaire MC, Alla F. Anaphylactic and Anaphylactoid Reactions Occurring during Anesthesia in France in 1999-2000. Anesthesiology 2003: 99: 536–45.

Mertes 2011: Mertes PM, Alla F, Tréchot P, *et al.* Anaphylaxis during Anesthesia in France: An 8-Year National Survey. J Allergy & Clin Immunol 2011: 128: 366–73.

De Pater 2017: Pater GH de, Florvaag E, Johansson SGO, Irgens A, Petersen MNH, Guttormsen AB. Six Years without Pholcodine: Norwegians Are Significantly Less IgE-Sensitized and Clinically More Tolerant to Neuromuscular Blocking Agents. Allergy 2017: 72: 813–19.

Reddy 2015: Reddy JI, Cooke PJ, Van Schalkwyk JM, Hannam JA, Fitzharris P, Mitchell SJ. Anaphylaxis is more common with rocuronium and succinylcholine than with atracurium. Anesthesiology 2015; 122: 39–45.

Sadleir PHM, Clarke RC, Bunning DL, Platt PR, Myles PS. Anaphylaxis to Neuromuscular Blocking Drugs: Incidence and Cross-Reactivity in Western Australia from 2002 to 2011. Br J Anaesth 2013: 110: 981–87.

Seed 2000: Seed MJ, Ewan PW. Anaphylaxis Caused by Neostigmine. Anaesthesia 2000: 55: 574–75.

Sury MRJ, Palmer JHMG, Cook TM, Pandit JJ. 2014. The State of UK Anaesthesia: A Survey of National Health Service Activity in 2013. Br J Anaesth 2014: 113: 575–84.

Tsur 2014: Tsur A, Kalansky A. Hypersensitivity Associated with Sugammadex Administration: A Systematic Review. Anaesthesia 2014: 69: 1251–57.