

Anaphylaxis during general anaesthesia: one-year survey from a British allergy clinic

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ABSTRACT

Introduction: Anaphylaxis during general anaesthesia is a major concern. Early recognition and management of anaphylaxis, as well as its future prevention, remain a challenge for the anaesthetists, while for the allergists, the elucidation of the causal agents may be difficult. We aimed to describe our experience in our drug allergy clinic.

Methods: We retrospectively reviewed 23 consecutive adult patients who presented with anaphylaxis during anaesthesia from March 1, 2005 to February 28, 2006.

Results: Out of the 23 patients (12 females, 11 males) with mean age (+/- SD) of 53.1 +/- 15.8 years, 15 patients were found to have a positive skin test to at least one neuromuscular blocking agent (NMBA); all of them showed cross-sensitivity with one or more NMBA(s). Three patients had a positive skin test to opioids, two patients to gelofusine, two patients to penicillin, and one patient each to povidone-iodine and chlorhexidine. Two patients had negative test results to agents used during their anaesthesia. Four patients had double positive skin tests to different families of drugs/agents. 18 patients had severe reaction-grade 3, and 15 of them tested positive for NMBA(s). Serum tryptase levels were known in nine patients. We did not encounter any latex or hypnotics sensitisation.

Conclusion: NMBA was the commonest cause of anaphylaxis during general anaesthesia, occurring in 65% in our series.

Keywords: anaphylaxis, drug allergy, general anaesthesia, neuromuscular blocking agents

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INTRODUCTION

Anaphylaxis during general anaesthesia (GA) is often severe and may be life-threatening. Clinical diagnosis is difficult as there is a need to differentiate from other causes of perioperative adverse reactions, such as side

effects of administered drugs, or patients' medical conditions which may present with bronchospasm or hypotension. Identification of the causal agents may also present a challenge to the allergist. Difficulties arise from patients receiving numerous drugs in rapid succession, and limitations in the allergy testing. Close cooperation between anaesthetists and allergists is essential to achieve proper diagnosis of the present adverse event, as well as prevention of its future recurrence. When comparing between countries, there are differences in the frequency of causal agents in perioperative anaphylaxis. This could be attributed to different populations, market share of the agents used,⁽¹⁾ as well as preoperative sensitisation.⁽²⁾ We describe our experience of patients attending our allergy clinic and compare it with other series.

METHODS

We retrospectively reviewed all patients who attended our allergy clinic from March 1, 2005 to February 28, 2006, a reference centre for anaphylaxis during general anaesthesia from the British Society of Allergy and Clinical Immunology (BSACI) and Anaesthetics Association of Great Britain and Ireland (AAGBI). We included patients who had anaphylaxis during the perioperative period, inclusive of reactions occurring during the recovery phase after surgery. We excluded patients who met one or more of the following conditions: (1) reactions with local or regional anaesthesia; (2) reactions occurring after the recovery phase of surgery; (3) referrals for predictive tests to future use of anaesthetic agents, without prior history of adverse reactions during anaesthesia; and (4) incomplete assessment or lost to follow-up. All patients were either referred by their respective general practitioners or specialists from other specialties, particularly anaesthesiology, usually after a recent adverse event during anaesthesia. Patients were evaluated based on history derived from various sources: patients themselves, surgeons' or anaesthetists' referral letters with or without accompanying copies of anaesthetic charts. In cases where further information was required, written correspondence was sent to the anaesthetist in charge of the operation(s). Patients' demographics, previous drug allergies and GA exposures, serum tryptase levels, as well as severity of reactions were documented. An elevated serum tryptase level was defined as more

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Table I. Clinical details of patients' demographics and drug allergy testing results

Patient	Age (years)	Gender	Time testing (months)	Serum tryptase (ng/ml)	Severity of reactions	Positive skin test to the following agent(s) (order of dilution)	Cross-reactivity	Remarks
1	43	M	3	NA	2	Povidone-iodine (3)	-	
2	36	F	6	69.6	3	Sux (3)	Cis	
3	60	F	6	42.5	3	Roc (2)	Vecu	
4	68	M	4	NA	3	Atra (1)	Cis	
5	51	F	5	NA	3	Vecu (4) / Sux (2)	Miva, Atra, Cis, Pan	
6	59	M	3	NA	3	-	-	Bronchospasm / COPD
7	31	M	17	20.4	3	Roc (2)	Sux, Vecu, Miva, Atra, Cis, Pan	
8	74	F	2	47.4	3	Roc (3)	Sux, Vecu, Cis	
9	55	F	84	NA	3	Atra (2)	Cis	
10	49	F	2	NA	1	Morphine (2) / Fentanyl (1)	-	
11	66	F	5	11.8	3	Roc (2)	Vec, Miv, Atra, Cis	
12	57	M	2	NA	3	Vec (3)	Atra, Miv	
13	63	F	4	84.0	3	Atra (2) / Sux (3)	Cis, Pan	
14	63	F	4	30.0	3	Vec (2) / Gelofusine (1)	Atra, Cis	
15	65	M	2	6.8	3	Gelofusine (2)	-	
16	21	M	3	NA	1	Atra (2) / Morphine (2)	Cis, Miv	
17	52	F	2	55.0	3	Penicillin	-	
18	28	F	3	NA	2	Atra (1)	Miva	
19	61	F	10	NA	1	Atra (2) and Morphine (2)	Miv	
20	66	M	26	NA	3	-	-	Hypotension secondary to rapid injection of high-dose remifentanyl
21	21	M	11	NA	3	Penicillin	-	
22	72	M	1	NA	3	Atra (1)	Miva	
23	61	M	13	NA	3	Chlorhexidine (3)	-	

Atra: atracurium; Roc: rocuronium; Vec: vecuronium; Cis: cisatracurium; Miva: mivacurium; Pan: pancuronium; Sux: suxamethonium; COPD: chronic obstructive pulmonary disease; NA: not available; M: male; F: female.

than 14 ng/ml (normal range 2–14 ng/ml), according to the normal values from the laboratory. The severity of the anaesthetic reactions was based on the grading system for generalised hypersensitivity reactions by Brown.⁽³⁾ Grade 1 reaction included skin/subcutaneous involvement (generalised erythema, urticaria, periorbital oedema, or angio-oedema); grade 2 reactions included respiratory, cardiovascular or gastrointestinal involvement (dyspnoea, stridor, wheeze, nausea, vomiting, dizziness, diaphoresis, chest or throat tightness, abdominal pain); and grade 3 reactions included hypoxia (oxygen saturation, SpO₂ ≤ 92%), hypotension (systolic blood pressure < 90 mmHg) or neurological compromise (confusion, collapse, loss of consciousness, urinary incontinence).

Patients were investigated usually no sooner than six weeks after the GA. Reactions were recorded using the intradermal testing (IDT) method according to the standardised procedures recommended by the SFAR (Société Française d'Anesthésie et de Réanimation) and the ENDA (European Network for Drug Allergy) guidelines.⁽⁴⁾ In summary, skin testing included all drugs listed in the anaesthesia record, latex and other agents administered during this procedure, with the exception of inhalational agents. The order of the testing was adapted according to the clinical history, the timing of the onset of the reactions in relation to the introduction of the drug, and the knowledge of incidence of allergy for each drug. The

skin test results were compared to a negative control with saline and positive control with histamine 10 mg/ml after interruption of the antihistamine treatment. We injected 0.03–0.05 ml of the convenient dilution of the commercial preparation into the dermis to produce an injection papule no larger than 4 mm in diameter. A positive test is defined by the appearance, after 20 min, of a wheal with a diameter of at least 8 mm and which is also at least double the diameter of the bleb produced by the injection.⁽⁴⁾

The maximum non-irritant concentrations of the various neuromuscular blocking agents (NMBA) were as follows: suxamethonium (1/500 dilution, 100 µg/ml), vecuronium (1/10 dilution, 400 µg/ml), pancuronium (1/10 dilution, 200 µg/ml), rocuronium (1/100 dilution, 100 µg/ml), cis-atracurium (1/100 dilution, 20 µg/ml), mivacurium (1/1000 dilution, 2 µg/ml) and atracurium (1/1000 dilution, 10 µg/ml). These concentration of each NMBA was designated as first-order dilutions. The second-order and the third-order dilutions would be the ten-fold and 100-fold dilutions from the maximum concentrations, and so forth. Whenever a patient was tested positive for a NMBA, cross-reactivity workup was performed with the remaining NMBAs from the above list. Regarding the other agents, the maximum concentrations used were as follows: morphine (1/1000 dilution, 10 µg/ml), fentanyl (1/10 dilution, 5 µg/ml), gelofusine (neat, 4% solution), chlorhexidine (neat, 0.05%), povidone-iodine (1/1000, 0.1

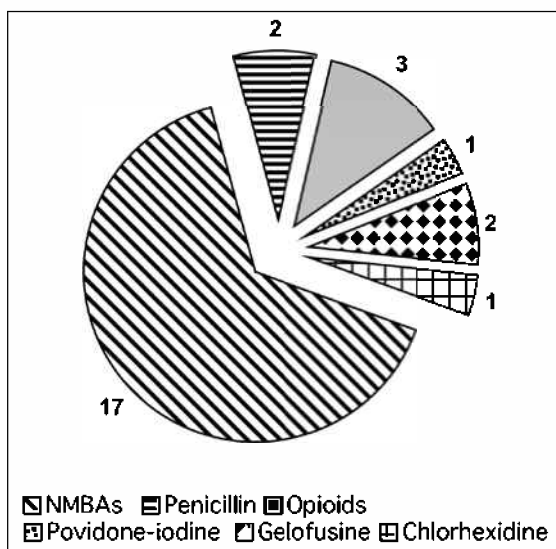


Fig. 1 Pie chart shows the number of positive skin test results among 21 patients.

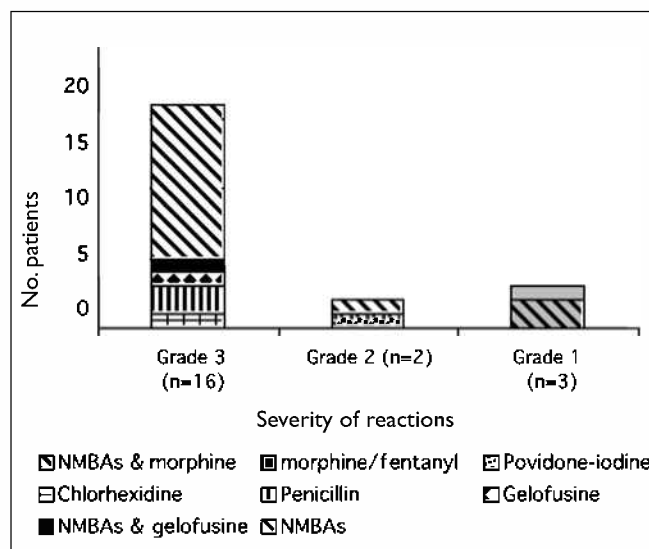


Fig. 2 Graph illustrates the severity of reactions in relation to 21 patients with positive skin test results.

mg/ml).⁽⁵⁾ Where appropriate, penicillin testing was done according to published guidelines.⁽⁶⁾

RESULTS

23 patients (12 females, 11 males) with a mean age and standard deviation of 53.1 ± 15.8 (range 21–72) years were identified (see Table I). 17 of them had a GA allergy assessment performed within six months of the anaphylaxis. The serum tryptase levels of 14 patients were unknown. Of the nine patients with known serum tryptase level, seven showed elevated tryptase levels (range 20.4–94.0 ng/ml). Two patients with normal tryptase levels suffered grade 3 reactions, which were the most severe in the classification.

15 patients with 17 positive skin tests to NMBA were identified. Two patients had positive skin tests to two NMBAs, which were both administered during the anaesthesia. Three patients were tested positive to opioids (two to morphine with both IDT positive at 1/10000 [second-order dilution]); one to both fentanyl and morphine at IDT positive to fentanyl at 1/10 (first-order dilution) and IDT positive to morphine at 1/10000 (second-order dilution), respectively; two patients had a positive test to penicillin (one to benzylpenicilloyl, one to amoxicillin); two patients had a positive test to gelofusine (IDT positive at 1/10 (second-order dilution) and neat (first-order dilution); and one each for povidone-iodine with IDT positive at 1/100000 (third-order dilution) as well as chlorhexidine with IDT positive at 0.005% (third-order dilution) (see Table I). In two patients, we could not determine any positive skin test. One patient had suffered bronchospasm from an underlying chronic obstructive pulmonary disease (COPD), while the other one was documented to have hypotension probably secondary to rapid injection of a high dose of remifentanyl.

Analysis of the 15 patients who had positive skin tests

to NMBA revealed seven patients who showed positive skin tests to atracurium, four patients to rocuronium, and three patients each to vecuronium and suxamethonium. These 15 patients were found to have at least one positive result of cross-reactivity to another NMBA. Positive skin tests to double agents were also found: morphine and NMBAs in two patients, concomitant morphine and fentanyl in one patient, and NMBA and gelofusine in one patient.

In terms of severity of reactions, 18 patients suffered grade 3 reactions. Of this, 12 patients were tested positive to NMBA(s). Two patients had reactions of grade 2 severity, and three patients had reactions of grade 1 severity. Among patients who had skin test positive to morphine three out of three were of grade 1 severity in terms of their reactions (Fig. 2).

DISCUSSION

In our series of 23 patients who suffered anaphylaxis during anaesthesia, we found NMBAs to be the causal agent in 15 (65.2%) patients. The next common causal agents are opioids in three (13.0%) patients, and penicillin and gelofusine in two (8.6%) patients each. In comparison, the results of the SFAR and ENDA group, which evaluated reactions of 4,000 patients during anaesthesia since 1980, showed that NMBA was the most frequent causal drug at 62%, followed by latex (16.5%), hypnotics (7.4%), antibiotics (4.7%), plasma substitutes (3.6%) and opioids (1.9%).⁽⁴⁾ However, we could not attribute any of our adverse reactions to latex or hypnotics. This is because this is a small series study and the order of frequency of our series may not be representative.

Skin testing with NMBAs and medical history are the usual clinical tools to diagnose IgE-mediated reaction to NMBAs. Controversy persists about the best method for skin testing of NMBAs, which are either skin

prick testing (SPT) or IDT. IDT has been used in the majority of studies, while some others used SPT. There is no common consensus regarding guidelines on the skin testing methods. Some recommend IDT for diagnosis,^(7,8) while for others, both methods are valid and optional,^(4,9) although some others recommend SPT.^(10,11)

The maximum concentrations which do not precipitate a nonspecific positive reaction among controls were defined for each drug according to the method of testing.^(4,12,13) In IDT, the lower the dilution a patient reacts to, the higher the chance of a real sensitisation or IgE-mediated mechanism, and the lower the risk of a false positive.

A few studies compared IDT with SPT. In a cumulative group of 259 patients, these studies observed a concordance a 92%–96% and 100% between the two methods.^(14,15) Discordant results were distributed between both methods with no excess in favour of the IDT, although it is generally considered more sensitive. Both methods comprised false positives and false negatives. Therefore, in order to confirm the results of skin testing, the gold standard will be to perform an incremental challenge test. However, due to the severity of the reactions occurring during GA, this was not done. Hence, sensitivity and specificity of skin testing to NMBAs were unknown. A false negative response may lead the patient to be exposed a second time to the same NMBA or a drug from the same family.^(16,17) On the other hand, a positive SPT to NMBAs was observed in 9.3% of nonallergic volunteers.⁽¹⁸⁾ False positives occur without specific IgE and may involve nonspecific histamine release with mast cell degranulation or irritant effect without mast cell degranulation.^(11,12) Apart from the skin test, there is no additional test available to diagnose NMBA allergy with higher sensitivity and specificity. Therefore, the testing method of choice in the first instance is based on factors such as age of the patient, cost, ease of performance and staff training. If the SPT is negative for the index NMBA, IDT should be performed and vice versa. The advice will then be to avoid the drug if any one of the methods is positive.

The commonly-published cross-reactivity rate between NMBAs is about 65%.^(19,20) In our series, all our patients had cross reactivity with other NMBAs upon further testing. One patient demonstrated cross reactivity to all tested NMBAs (patient 7 in Table I). However, upon closer examination, we found that all of this patient's cross reactivity were positive for first-order dilutions only. Therefore, we doubt these were true cross sensitisations, although for clinical safety, the advice was to avoid those NMBAs.

In our series, 11 out of 12 patients monosensitised to NMBAs suffered from grade 3 reactions. We observed two patients with positive skin tests to both atracurium and

morphine. Both of them had grade 1 mild reactions. As reactions to NMBAs were usually of grade 3 severity, this made us suspect morphine as the main agent responsible for the reactions. The positive skin test to morphine is poorly reliable and reaction to morphine is more often a nonspecific histamine release.⁽²¹⁾ Therefore, it would be more useful and informative to perform an incremental challenge with morphine on these patients.

There were two patients with positive skin tests to gelofusine, which accounted for 8.6% of the total general anaesthetics reactions in our series. SPT to neat gelofusine were negative in both patients. As the reactions of both patients were of grade 3 severity and showed clear causal-reaction temporal sequence, we proceeded with IDT with gelofusine as described previously.⁽²²⁾ Both patients showed positive results with IDT with gelofusine, and one of them kept the positive result up to 1:1,000 dilution intradermally. In the literature, both SPT and IDT were suggested diagnostic approaches.^(13,23) In our experience, we found IDT to be more informative than SPT.

We had one patient who suffered generalised urticaria and angio-oedema during an orthopaedic operation, where application of povidone-iodine to an open wound was performed. This patient had positive SPT to povidone-iodine (Videne[®], Adams Healthcare, Leeds, UK) at concentrations of 1/1,000 (0.1 mg/ml) up to 1/100,000 (0.01 mg/ml). Sensitisation to other drugs he had received during the general anaesthesia and surgery (midazolam, fentanyl, propofol, morphine) were ruled out by negative IDT results to different concentrations following the ENDA guidelines.⁽⁴⁾ He also showed a negative SPT result to latex. Further evaluation with neat aqueous iodine (Lugol's solution, total iodine content, 130 mg/ml) was negative, thus enabling us to surmise that the allergic reaction was provoked by the povidone component, which is a carrier molecule for iodine atoms. Sensitivity to povidone is rare, although it has been reported previously.^(24,25) There is no evidence supporting allergy to iodine. This has recently been reviewed by Sicherer on behalf of the Adverse Reactions to Foods Committee and the Adverse Reactions to Drugs and Biological Committee of the American Academy of Allergy, Asthma and Immunology (AAAAI), New York; in addition, there is no cross reactivity with iodine contrast media or seafood.⁽²⁶⁾

One patient (patient 23 in Table I) who was found to be allergic to chlorhexidine, was exposed to the antiseptic during his orthopaedic surgery. Close re-questioning of his previous medical history revealed mouth pruritis and lips swelling upon using a chlorhexidine mouthwash many years ago. There is also evidence that anaphylaxis to chlorhexidine could be preceded by chlorhexidine-induced contact dermatitis years ago.⁽²⁷⁾

We observed no sensitisation to latex, despite

systematic testing of all our patients. Systematic consecutive surveys from the French series showed latex to be the second most frequent cause of perioperative anaphylaxis since 1990.⁽⁶⁾ Latex sensitisation is associated with atopy and cautious preoperative history evaluation allows the identification and diagnosis of most cases of latex sensitisation.⁽²⁵⁾ Preoperative assessment for latex sensitisation is efficient in reducing the incidence of latex-associated anaesthetic reactions. Atopy is, however, not a risk factor for sensitisation to NMBAs or most drugs used during anaesthesia. Bronchial asthma does not increase the frequency of anaphylaxis during anaesthesia, but is a risk factor for severe symptoms.⁽²⁷⁾

Serum tryptase is an indicator of mast cell degranulation and tends to be elevated within hours in both IgE-mediated anaphylaxis and non-IgE mediated anaphylaxis. It is helpful in confirming the diagnosis, particularly if a patient presents with bronchospasm or hypotension from a concurrent illness. In our study, we were able to obtain serum tryptase in nine patients. We encountered two patients who presented with symptoms mimicking perioperative anaphylaxis. The first patient developed respiratory failure with hypoxia and wheezing with a background of COPD, while the second patient had severe hypotension in the background of congestive cardiac failure with rapid injection of high dose remifentanyl. Thorough evaluations with all the GA drugs administered yielded no culpable agents in both patients. A negative serum tryptase level would be useful to exclude anaphylaxis in these instances.⁽⁸⁾

In conclusion, our study showed NMBAs to be the commonest cause of anaphylaxis during general anaesthesia. We observed no anaphylaxis due to latex allergy. Systematic measurement of serum tryptase not only helps to confirm the diagnosis of anaphylaxis which occurs during anaesthesia, but also to exclude it whenever there are doubts or when the reactions are atypical.

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