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REVIEW

Anaphylaxis associated with general anaesthesia: Challenges and recent advances

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S U M M A R Y

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A proportion of severe adverse reactions associated with general anaesthesia are due to allergic or non-allergic anaphylaxis to one of the anaesthetic drugs, most commonly the neuromuscular blocking agents (NMBA's). Patients with suspected anaphylaxis should be referred to a specialist clinic for further investigation, the aim of which is to determine the nature of the reaction, the causal agents, and safe alternatives which may be used.

The single most important factor in reaching a diagnosis is the temporal relationship between drug administration and the onset of symptoms; serum tryptase and skin tests are then used support or refute the clinical diagnosis.

Although NMBA's are still the commonest cause of perioperative anaphylaxis, other agents such as antibiotics, medical dyes and chlorhexidine have been increasingly recognised.

Future efforts are focused on improving the accuracy of current diagnostic tests and on the development of new methods to identify patients at risk of allergic reactions to anaesthetic drugs.

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1. Introduction

Common definitions of anaphylaxis include “a serious, life-threatening generalised or systemic hypersensitivity reaction” and “a serious allergic reaction that is rapid in onset and might cause death.”¹ The clinical manifestations defining this syndrome result from release of preformed and de-novo synthesised biochemical mediators, including histamine released from tissue mast cells and blood basophils. In the context of general anaesthesia (GA), anaphylaxis can result from hypersensitivity to any of the agents administered in the perioperative period. Patient factors such as concomitant disease and medications, particularly those which affect mast cell stability, can influence the likelihood and severity of anaphylaxis.

This review aims to provide an overview of the steps involved in recognition, investigation and diagnosis of perioperative anaphylaxis as well as common problems encountered in this process. The causes of anaphylaxis will be explored with an emphasis on drugs which have more recently emerged as causal agents. Finally, we will discuss future areas of research in the recognition and diagnosis of anaphylaxis.

1.1. Incidence and recognition of perioperative anaphylaxis

Anaphylaxis associated with general anaesthesia (AAGA) is a rare but important cause of morbidity and mortality in the perioperative period. Mortality is quoted at 3–9%, although this is generally considered to be an underestimate as a consequence of poor reporting pathways.^{2,3} No clear data exist for morbidity rates, but in one case series, 2% of patients were reported to have significant residual brain damage.⁴ The reported incidence of reaction varies worldwide, with higher rates in the UK, New Zealand, Australia and France. It is generally quoted at 1 in 13,000 to 1 in 1380 anaesthetics.⁵ Published studies from the US in 2010 demonstrated under-diagnosis and inadequate investigation of allergic reactions.⁶ The largest study performed to date in this field is an eight-year, multicentre study in France, completed in 2011. Around 2500 patients were investigated, with an incidence of AAGA found to be 1 in 10,000. Of particular interest, they noted a higher incidence among female compared to male adults, but no sex differentiation within the paediatric population and postulated that sex hormones may play a role in the sensitization of individuals to allergic reactions. Similarly to studies from the US, Mertes reported that there is significant under-reporting of anaphylaxis.⁷ This can potentially result in further harmful exposure to causal agents as well as the harmful avoidance of agents which are safe for an individual.

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Failure to recognize and report allergic reactions is likely to be multifactorial. With the exception of angioedema, clinical signs often appear in isolation (e.g. isolated bronchospasm or hypotension) rather than part of a more obvious syndrome.⁷ In these circumstances, the clinical findings may be thought to represent an exaggerated physiological response to anaesthesia or surgery; for example isolated hypotension as a response to induction, or bronchospasm due to manipulation of the airway. The absence of cutaneous signs can also be misleading although this is a relatively common finding in anaphylaxis. Mertes found that around one third of IgE-mediated reactions demonstrated no cutaneous signs.⁷ Indeed this may reflect a more severe and rapidly progressing reaction, with cardiovascular collapse and loss of subcutaneous vascular perfusion.⁸ The diagnosis of hypersensitivity may also be delayed in the setting of massive hypovolaemia due to a paradoxical bradycardia (Barold–Jarisch reflex). This has been documented in around 10% of patients suffering anaphylaxis.³

Even when an adverse event is recognised as potential hypersensitivity, this may not be reported, particularly if the clinical signs resolve rapidly and surgery progresses uneventfully. There are several perceived barriers to reporting such events, particularly relating to uncertainty about the referral pathway. The guideline published by Association of Anaesthetists of Great Britain and Ireland (AAGBI) provides practical advice to help with recognition of AAGA and referral of suspected cases to specialist clinics.³

2. Principles of investigations and diagnosis of AAGA

All patients with suspected AAGA should be referred to a specialist centre for further investigations (Fig. 1). The cause may be multifactorial, including both immunological and non-immunological factors, and combined input from allergists (immunologists) and anaesthetists is generally recommended to provide a comprehensive assessment. The investigation of AAGA aims to determine the nature of the reaction, and the agents which should be avoided or which are safe to use in the future.

Historically, ‘anaphylaxis’ referred only to IgE-mediated reactions and the term anaphylactoid was used for reactions resulting from direct mast cell degranulation. However, these two entities are clinically indistinguishable since their presentation may be identical and the immediate treatment is the same. Both pathways can lead to potentially overwhelming histamine release with consequent cardiovascular instability and respiratory compromise. The preferred terms are therefore allergic and non-allergic anaphylaxis, respectively indicating IgE and non-IgE mediated mast cell degranulation.

2.1. Is it anaphylaxis?

The investigation of AAGA is directed toward answering two key questions. Firstly, was the adverse reaction due to a histamine-releasing event, or was it simply the result of an exaggerated physiological response to anesthetic or surgical manipulation? Secondly, if anaphylaxis has occurred, was the underlying mechanism IgE-dependant or independent? The most useful investigation to help answer the first question, and the only test which needs to be performed in the acute situation, is the serum level of mast cell tryptase (MCT). Following a hypersensitivity reaction, serum concentration of MCT peaks at 15 min to 1 h, then declines rapidly (following first order kinetics). The half life is around two hours. Persistently elevated levels at 24 h may indicate a systemic mastocytosis,⁹ which if present might be the cause of suspected anaphylaxis. A study of 350 patients with suspected AAGA found that elevated MCT was significantly associated with sensitisation to the drugs implicated in the reaction; conversely fewer than 1% of patients with normal MCT levels had evidence of sensitisation.¹⁰ The largest study to date investigating the role of MCT in diagnosis of AAGA, found it was much better at detecting anaphylaxis (positive predictive value 93%), than excluding it (54% negative predictive value).¹¹ These findings were replicated in a much smaller Scandinavian study.¹² MCT may also be useful in post-mortem studies, where serum MCT levels are normally slightly

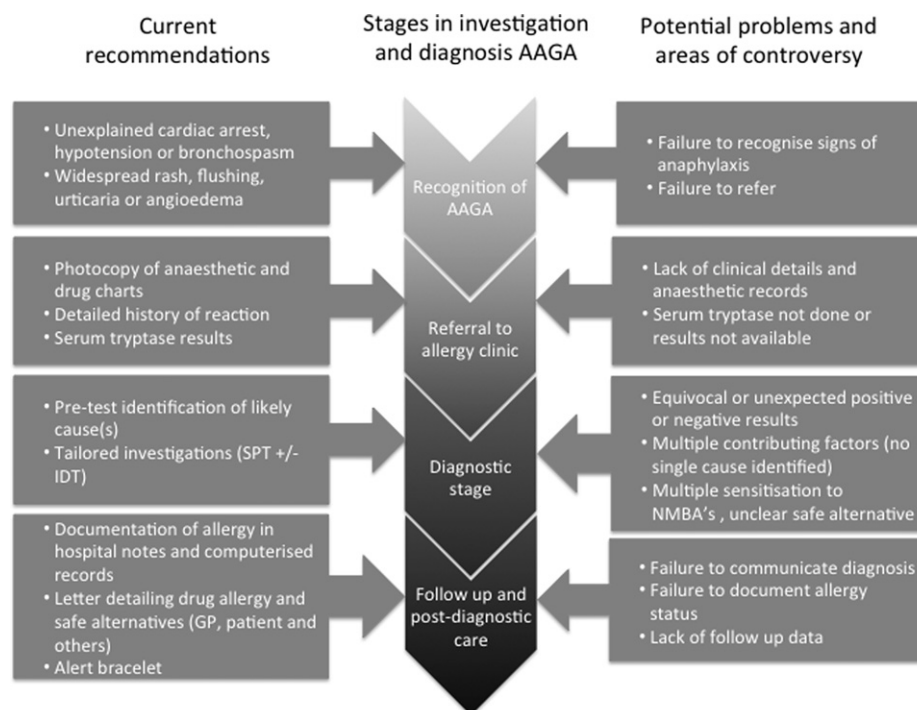


Fig. 1. Overview of diagnostic pathway for investigation of AAGA.

raised, but very large increments are highly indicative of fatal anaphylaxis.¹³

Urinary histamine is another potential marker of mast cell degranulation. However it is less sensitive than MCT and due to its much shorter half-life the test is more difficult to perform and not routinely available.¹⁴ When MCT levels from the time of the event are unavailable this can cause significant difficulties in reaching a diagnosis.

2.2. Allergic or non-allergic anaphylaxis

In IgE-mediated reactions a sensitisation event generally precedes the development of anaphylaxis. Initial exposure to the allergen results in the (asymptomatic) production of IgE isotype antibodies (Ab) which bind high-affinity Fc receptors (FcεRI) on tissue mast cells. On re-exposure, the allergen causes mast cell degranulation by binding to the receptor-bound allergen (drug)-specific IgE (sIgE) Ab. In non-IgE mediated hypersensitivity reactions, the drug causes direct mast cell degranulation.

Distinguishing between allergic and non-allergic anaphylaxis can be challenging. Detection of sIgE Ab does not prove causality and is not necessarily predictive of future reactions^{15,16}; furthermore the tests routinely used to demonstrate sIgE Ab in vivo [skin prick (SPT) and intradermal (IDT)] are themselves imperfect. The sensitivity and specificity of SPTs and IDTs is unknown since it is impractical to confirm the diagnosis with incremental drug challenge testing when there is strong clinical suspicion of allergy. These tests therefore remain unvalidated. This problem is further compounded by a lack of universally agreed criteria on the drug dosage and dilution used in skin tests. Further diagnostic confusion arises with drugs such as atracurium and rocuronium which are capable of causing mast cell degranulation in both an IgE-dependent and non-dependent fashion.

Skin tests are ideally used to support or refute a diagnosis which is determined by the clinical setting at the time of the reaction. This involves a detailed examination of the anaesthetic chart and notes

to establish the timing of all drugs given in relation to the onset of signs. Anaphylaxis to agents given at induction such as neuromuscular blocking agents (NMBAs) tends to occur rapidly following the intravenous administration of a large bolus of allergen; agents such as latex, and chlorhexidine tend to cause a reaction more slowly (Fig. 2). This reflects slower entry of the allergen to the circulation via skin and mucous membranes. Chlorhexidine-impregnated central venous catheter typically causes a more immediate reaction.

The patient's medical history is important since pre-existing conditions may mimic or exacerbate symptoms and signs of anaphylaxis; for example bronchospasm may be more pronounced during anaphylaxis in an asthmatic. A previous history of reaction to non-anaesthetic drugs may suggest increased risk of sensitisation to common anaesthetic drugs such as NMBAs.¹⁷

The diagnostic limitations of skin tests, and potential risks of anaphylaxis with IDT, have led to attempts to detect sIgE Ab in serum rather than skin. These include solid-based immunoassays and cellular-based tests such as the basophil activation test (BAT). Suxamethonium is the only NMBA for which there is a commercially available specific immunoassay; unfortunately its sensitivity is poor, at between 30 and 60% (2007 Ebo). All NMBAs contain substituted ammonium groups and quaternary ammonium ions in their structure, which are the main allergenic epitopes recognised by sIgE.¹⁸ Since the describing of these structures around thirty years ago, various substrates have been developed to mimic them for use in immunoassays.¹⁹ Novel immunoassays, based initially on tertiary ammonium group of morphine and more recently on quaternary ammonium morphine, have shown sensitivities of 84% for the detection of NMBA sIgE's.²⁰ Other commercially available immunoassays of interest include those for thiopentone, propofol common antibiotics (amoxicillin, cefaclor, penicillin G and V), latex and chlorhexidine.

BAT is technically more demanding and not routinely available. Basophils, like mast cells, have FcεRI which can bind sIgE. BAT quantifies the expression of basophil activation markers such as

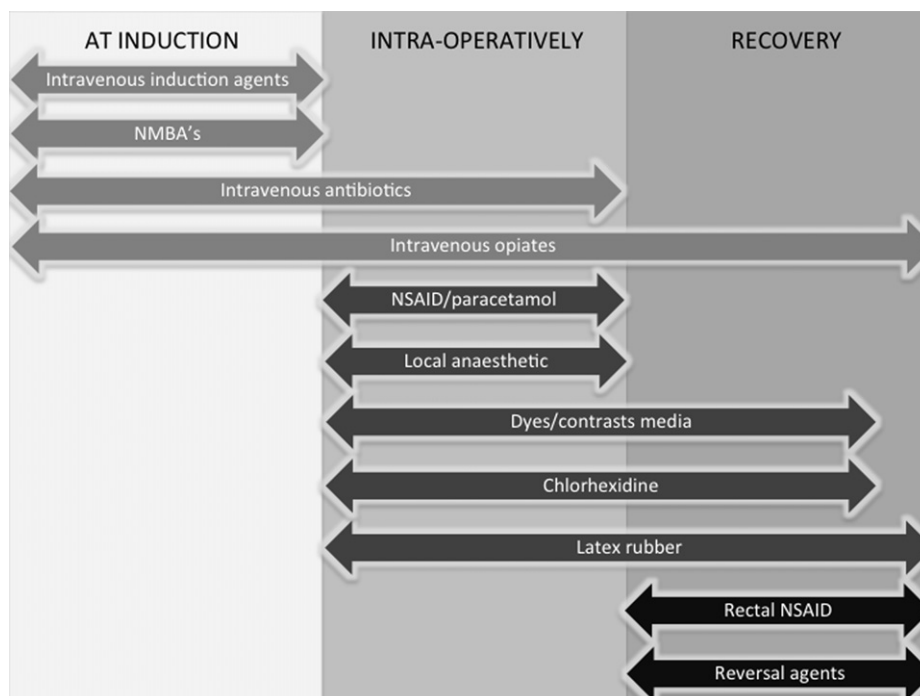


Fig. 2. Relationship between timing of adverse reaction and potential causes NMBA's tend to cause reactions within minutes of induction. Antibiotics and opiates can be administered at various stage of procedure.

CD63 and CD202c following incubation with the drug of interest. This method has demonstrated very high specificity, sometimes 100%, but has low sensitivity. As with the immunoassays its use is as an adjunct to skin tests rather than a replacement for them.

Occasionally, no conclusive diagnosis is reached despite extensive investigation. In such cases, the adverse event may simply reflect the convergence of several risk factors. For example, a septic patient receiving regular non-steroidal antiinflammatory drugs who then undergoes major surgery, might be at greater risk of non-allergic anaphylaxis due to administration of mast cell destabilising drugs, than a well patient taking no medications having an elective procedure.

2.3. After diagnosis

There is very little follow-up data on patients who have been diagnosed with an allergy to one or more anaesthetic agents. In a study of 606 AAGA patients in Australia, more than half were lost to follow up.²¹ However, they noted that 183 patients (of the 246 whose notes were available) had been safely anaesthetised following clinic attendance, although only 11 of these had had their notes updated with details of the drugs given. The same authors published earlier work showing that in 52 patients for whom no cause for the reaction was found, 51 went on to have uneventful anaesthesia, and of 301 patients for whom a cause was found, 295 had subsequent uneventful anaesthesia.²² Since it is not known what agents were used during subsequent anaesthetics the accuracy of the clinic diagnosis cannot be proven. The authors also noted that more than 50% of patients who had been given a medical-alert type bracelet were not wearing them when they attended for recall clinic visits. They have since introduced new strategies to improve the flow of information – the most important of which was to encourage the patient themselves to ‘become the custodian of their information’. In the current absence of nationalised databases which can be accessed at all hours, this approach may also need to be adopted in the UK.

3. Common and some less common causes of AAGA

Traditionally, the agents most often responsible for allergic anaphylaxis were the NMBA, antibiotics and latex, and this remains largely the case today. In the eight-year study in France they made up 60%, 20% and 10% respectively, of all immune-mediated reactions.⁷ However the relative frequency with which causal agents are identified is changing. Latex allergy has decreased in the UK with the greater use of latex free equipment in theatres.^{3,14} Conversely, antibiotic related anaphylaxis is increasing, which may reflect more widespread use for prophylaxis. Newer agents are seen with increasing frequency, which may be a reflection of changing medical practice and of increased exposure of the public to environmental sensitizing agents.

3.1. Neuromuscular blocking agents

NMBAs can cause allergic anaphylaxis without sensitisation through previous NMBA administration. Indeed a significant proportion of patients who develop anaphylaxis do so on their first exposure to the drug and the sensitizing agent remains unknown.¹⁸ However, many commonly used products such as cosmetics, shampoos and cough medicines, contain quaternary ammonium ions in their chemical structure which are similar to those found in NMBA's. It has been suggested that their use may result in sensitisation to the NMBA. An example of this was seen with the use of pholcodine, which contains a quaternary ammonium ion. This cough suppressant is freely available over the counter in Norway

where there is a greater incidence of NMBA allergy compared to Sweden where pholcodine was not in routine use.²³ A later study performed across nine different countries also showed an association between pholcodine consumption, and the greater prevalence of IgE's to pholcodine (and morphine), which cross-react with NMBA's.²⁴ The so-called ‘pholcodine hypothesis’ gained further support when incidence of NMBA allergy fell significantly in Norway after withdrawal of the drug.²⁵

Within the NMBA group, suxamethonium is traditionally the agent most frequently found to cause anaphylaxis. However, there has also been a surge in recent years of cases caused by rocuronium, which appears to be more allergenic than the other non-depolarising agents. The reasons for this are not clear, but may reflect biased adverse drug reaction reporting in a relatively new drug or a significant increase in usage in recent years, rather than a greater tendency of the drug to cause anaphylaxis.⁷

A novel method to treat allergic anaphylaxis to rocuronium has recently been proposed, with anecdotal evidence suggesting that sugammadex may attenuate the IgE-mediated hypersensitivity reaction. Sugammadex is a cyclodextrin which causes rapid reversal of rocuronium-induced neuromuscular block by encapsulating free rocuronium molecules as inclusion complexes.²⁶ Several case reports have described the use of sugammadex after presumed anaphylaxis to rocuronium, often with a striking temporal relationship between administration of sugammadex and rapid resolution of the signs of hypersensitivity.^{27,28} However when 11 patients with known IgE mediated hypersensitivity to rocuronium were skin prick tested with rocuronium followed sequentially by sugammadex, the administration of sugammadex did not appear to modify the course of the already established hypersensitivity reaction.²⁹ It was noted however that if rocuronium was pre-incubated with the sugammadex prior to injection, hypersensitivity was prevented altogether. This clearly has no merit in a clinical setting. Furthermore, there are a few case reports of confirmed hypersensitivity to sugammadex itself,³⁰ which may discourage further off-license use in rocuronium-associated allergy.

3.2. Diagnostic dyes

A group of drugs increasingly seen to cause hypersensitivity are the medical blue dyes, and in particular patent blue v. Incidence rates for patent blue v and isosulfan blue are quoted at between 0.24% and 2.7%.³¹ Reactions are often noted to be severe and to persist for several hours.^{32,33} Methylene blue causes hypersensitivity much more rarely and may be a good alternative to the other dyes, although it is can result in skin necrosis and ulceration. Previously low incidence rates in the literature may stem from the confusing nomenclature of medical dyes, making literature reviews of the subject inherently more difficult.^{32,34} Patent blue V, for example, is also known as acid blue 3, disulphine blue, and as the food additive E131 (It should also not be confused with patent blue violet, the alternative name for isosulfan blue). In addition, the unusual temporal relationship between administration of the drug and the onset of symptoms may lead to the mis-attribution of a reaction to another drug. The reaction may be seen within 15 min of administration, but is more commonly seen at 30–60 min; a case series of 14 patients gave a mean time of 30 min.^{7,35} This is a similar problem to that seen in diagnosis of chlorhexidine allergy.

Anaphylaxis to patent blue v, which is used with increasing frequency in sentinel lymph node biopsies (SLNB), is most likely to be an IgE-mediated phenomenon.^{33,35–37} Previous sensitization may be the result of exposure to the drug in food and chemicals, or to previous SLNB. Prior treatment with steroids and antihistamines may dampen the reaction (particularly for those cases which are actually non-immune mediated) but does not reduce the

incidence.³² Skin prick testing is positive for most but not all patients whereas intradermal testing has 100% sensitivity.^{32,35,37} Where hypersensitivity has been established, it is prudent to check for cross-reactivity with alternative agents such as isosulfan blue and methylene blue, in case repeated biopsies are required.

3.3. Chlorhexidine

Chlorhexidine allergy is appearing with increasing frequency in anaesthetic allergy clinics. Thus far there are several case reports of anaphylaxis but no large case series. Anaphylaxis to chlorhexidine also appears to be IgE-mediated³⁸ and can be associated with severe reactions. As with the blue dyes, a delayed onset of symptoms and signs can be misleading; slow absorption through the skin results in symptoms typically developing 10–30 min after application. Chlorhexidine-impregnated devices such as central venous lines, and the use of Instillagel (containing chlorhexidine as the active ingredient) can result in faster onset due to their more invasive nature.^{39–41} There is concern about sensitization in health care workers who are regularly exposed to the drug. A study in 2009 found high levels of sensitization in health care workers and recommended that this differential is included in the investigation of occupational allergy.⁴²

3.4. Less common causes

Agents less commonly associated with anaphylaxis include the hypnotics, opioids and colloids. The classic anaesthetic concern of egg allergy and propofol administration is likely to be over cautious. A study in 2011 demonstrated the safety of propofol in children with proven egg allergy and concluded there was little risk of allergic reaction.⁴³

Local anaesthetic allergy, which is frequently self reported by patients, is in fact vanishingly rare. The ester group of local anaesthetics which used to be responsible for some cases have now been largely replaced by amide local anaesthetics, which are even less allergenic. The Mertes study revealed an incidence of IgE mediated reaction of 0.3%,⁷ whilst a review in 2012 gave an incidence of 0.97%.⁴⁴

4. Future studies

Severe reactions to drugs are usually unpredictable and occasionally have fatal consequences. In terms of immunologically mediated reactions some progress has been made in identifying individuals who might be at risk. This work has mainly been in relation to delayed-type reactions which are not mediated by sIgE, but by cellular components of the immune system such as drug-specific T (sT) cells. An association has been established between HLA-type, which dictates how different antigens including drugs are presented to the immune system, and hypersensitivity to a number of drugs. To date the following associations have been recognized: abacavir and HLA-B*57:01,⁴⁵ carbamazepine and HLA-B*15:02/A*31:01⁴⁶ and finally allopurinol and HLA-B*58:01.⁴⁷ In the case of abacavir it is now common practice to perform an HLA gene screen before commencing treatment. Since sensitisation of an individual may also depend on HLA type, similar studies might also be useful in predicting those at risk of immediate-type (sIgE-mediated) reactions to anaesthetic drugs.

5. Conclusion

The investigation of AAGA can be challenging but is often very rewarding. Many advances have been made and guidelines are now in place to help with the recognition, referral and diagnosis of such

events. The most important tools in this process nevertheless remain a detailed clinical history and experienced investigators. To improve the accuracy of current diagnostic methods, a culture of robust incidence reporting and follow up data collection is needed.

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