

Anaesthesia-related anaphylaxis: investigation and follow-up



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Key points

Type I hypersensitivity reactions during anaesthesia occur rapidly after exposure to the trigger agent and can present with atypical features.

Suspected allergic reactions should be referred for prompt follow-up to identify safe agents for future use.

Investigation involves consideration of timing of exposure to all potential precipitants, clinical features, skin tests, blood tests, and occasionally challenge testing.

Prior exposure to the trigger agent, particularly neuromuscular blocking agents (NMBA), is not always required for sensitization to take place.

Cross-sensitivity between NMBAs is common and this may occur between drugs that are members of different chemical families.

Accurate record keeping, patient record alerts, arranging appropriate follow-up, and clear patient communication are essential.

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The AAGBI working party on anaphylaxis recently published excellent guidelines.¹ This article focuses on practical follow-up after anaphylaxis with case examples.

Adverse drug reactions are a common cause of anaesthetic-related morbidity and mortality in healthy patients. They include drug intolerance or immune-mediated reactions, including anaphylaxis.

Anaphylactic or anaphylactoid/ allergic or non-allergic

The European Academy of Allergy and Immunology (EAACI) redefined anaphylaxis as a severe, life-threatening, generalized, or systemic hypersensitivity reaction, sub-divided into 'allergic' and 'non-allergic' reactions.

Allergic anaphylaxis has an incidence between 1/5000–1/20 000 with a 3:1 female preponderance. Despite initially increased reporting of adverse events to new drugs (Weber effect), there is generally under reporting to databases (e.g. the UK yellow card system). Anaphylaxis-related mortality is 3–6% and an additional 2% have a poor neurological outcome.²

Allergic anaphylaxis implies an immunological reaction (IgE, IgG, or complement mediated). Antigen exposure results in mast cell and basophil bound antibody formation. Subsequent antigen exposure causes mast cell degranulation and the release of mediators including histamine, tryptase, leukotrienes, and prostaglandins. In 'non-allergic' reactions, mast cell and basophil degranulation are caused by direct drug action with no immune trigger. The term 'anaphylactoid' is now obsolete and encompassed non-IgE-mediated and non-allergic reactions.

The immunological mechanism is important as skin prick testing identifies only IgE-mediated hypersensitivity. Lack of skin changes does not necessarily exclude a drug as the allergic trigger.

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Immediate management

The features and immediate management are described in the AAGBI document found at http://www.aagbi.org/sites/default/files/anaphylaxis_2009_0.pdf. Anaesthetists should remain familiar with the 'anaphylaxis drill'.

Who should be referred for investigation?

Identifying causal agents is difficult and in 40% of cases the suspected allergen turns out to be incorrect. Investigation is indicated in the following:

1. Patients with a history of anaphylaxis or unexplained reaction during previous anaesthesia, including cardiac arrest, hypotension, bronchospasm, urticaria or rash, and angioedema.
2. Patients with a documented allergy to neuromuscular blocking agents (NMBAs). Cross-sensitivity should be explored.
3. Patients who allege an allergy to local anaesthetics (LAs) when local anaesthesia is scheduled.

A history of suspected latex allergy that is unequivocally positive does not require further investigation. All patients must be informed verbally and in writing. Referrals should include details of the suspected reaction including anaesthesia records, notes, and mast cell tryptase (MCT) results. The anaesthetist involved is responsible for the referral and the AAGBI website has details of referral centres and forms.

Investigating the reaction

Investigation aims to identify the nature of a reaction, the causative agent, and a plan for future anaesthesia. It involves a detailed history supported by skin and blood tests and occasionally careful drug challenges.

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History

The following are important:

1. All agents to which the patient was exposed (including latex, antiseptics, and infusions) with associated timings. Type I reactions typically occur within seconds to minutes after i.v. exposure. An insidious or delayed onset may occur (e.g. with latex, antibiotics, and colloids¹ and a tourniquet may delay onset until after surgery).
2. Additional interventions including central line and urinary catheter insertion.
3. Past anaesthetic records are helpful but previous exposure to drugs is not always necessary.
4. An allergic history including atopy, asthma, and known drug and food allergies. Atopy is a hereditary predisposition in which IgE antibodies are synthesized to various environmental allergens and has a clear link with latex allergy.³ It is also a risk factor for NMBA sensitivity.

Environmental allergen exposure is important. Quaternary amine groups in household products like toiletries and detergents share allergenic epitopes with NMBAs. The cough medicine pholcodine may be associated with an increased incidence of NMBA allergy through a higher prevalence of IgE antibodies to succinylcholine.⁴ There is a higher rate of antibiotic allergy in smokers, and some fruits and nuts exhibit cross-reactivity with latex hypersensitivity.

Mast cell tryptase

MCT is a protease enzyme with two subtypes alpha and beta. Alpha and pro-Beta are secreted constitutively by tissue-bound mast cells and mediate intestinal and bronchial smooth muscle relaxation. Mature β -tryptase stored in granules is released during anaphylaxis and stimulates the release of pro-inflammatory mediators. MCT has a half-life of 2 h, peaking at 1 h after anaphylaxis onset. Typically the increase is less marked in non-allergic reactions. A relative change is more significant than absolute concentration as baseline plasma levels vary. Levels may be elevated during high physiological stress (e.g. hypoxaemia or myocardial infarction and in patients with systemic mastocytosis). Normal tryptase results do not exclude anaphylaxis and can be seen in serious reactions. They can occur in basophil or complement-mediated reactions and fluid infusions can dilute plasma MCT. MCT is preferred to histamine whose half-life is too short to be useful.

Skin testing

This includes skin prick (SPT) and intradermal (IDT) testing. Skin testing is usually carried out 4–6 weeks after a reaction to allow replenishment of histamine in mast cell granules. It can be undertaken sooner, with the risk of misleading negative results. Antihistamine drugs must be stopped for 5 days though steroids may be continued. Paired tests are performed on the volar aspect of the forearm.

During SPT a drop of undiluted drug is used though some drugs are diluted to minimize direct skin histamine release. The skin is pricked with a lancet and is read after 15 min. Positive and negative controls are used using histamine and saline, respectively. A wheal of >3 mm in diameter than the negative control is considered positive⁵ and the presence of a flare or itching is also significant. SPT is highly sensitive for NMBAs and gelatins but insensitive for barbiturates, benzodiazepines, and opiates.

IDT is indicated if there is clinical suspicion but negative SPT. A 4-mm bleb of diluted solution is injected under the skin and read after 15 min by measuring the wheal and flare. IDT is considered positive if the bleb doubles or exceeds 8 mm. The AAGBI suggests that IDT are more sensitive but less specific than SPT.¹ Specific drug dilutions are important in determining the usefulness of IDTs. For NMBAs, the sensitivity of these tests is between 94 and 97% though the diagnostic yield of SPT compared with IDT may be no different.⁶

Skin testing identifies IgE-mediated reactions but is less helpful for nonsteroidal antiinflammatory drugs (NSAIDs), dextrans or radiocontrast media. As far as antibiotics are concerned, skin testing is particularly useful for antibiotics of the beta lactam group but of limited value for other antibiotics. Although skin prick testing will only identify IgE-mediated reactions, intradermal testing has the advantage of also identifying delayed hypersensitivity reactions. This is particularly important for allergies to LAs. However, in this situation the test may become positive up to several hours later. Drugs with direct histamine-releasing properties, such as morphine, make SPTs difficult to interpret through false positives. Most anaesthesia-related drugs, NMBAs, β -lactam antibiotics, latex, protamine, and chlorhexidine can be tested. Skin prick testing is safe, but intradermal injections may rarely precipitate systemic reactions.

The interpretation of skin tests can be difficult. Patients demonstrate variable cutaneous inflammatory reactivity and dermatographia can be problematic. Where false positives occur patients may be denied drugs inappropriately. Negative SPT and IDT makes clinically significant allergy less likely but false negatives can occur (e.g. a non-IgE-mediated mechanism). A drug with a high clinical suspicion but negative testing should still be avoided. For example, skin testing for antibiotic allergy is only 60% predictive of clinical hypersensitivity. Combining skin tests with IgE assays may help improve accuracy. Ultimately, clinical judgements are based on all available information, including history, drug timings, and skin testing.

Challenge testing

Drug challenging is the only way to exclude clinical allergy. It may be indicated when skin tests are unhelpful (e.g. NSAIDs, opiates) or when there is a clinical need for a drug in the future. Challenging carries a risk of precipitating anaphylaxis. Patients should be consented, fully monitored, with i.v. access. Challenging involves a graded exposure from small to clinically relevant quantities orally, subcutaneously, or intravenously. If at any point there are signs of hypersensitivity the testing is stopped. Where there is a strong

suspicion of a drug causing anaphylaxis, challenging should not be undertaken. Diagnosing allergy to LAs can only be made if a challenge test is positive.

Blood tests

Radio immunoabsorbent testing (RAST)

RAST has been superseded by a fluorescent detection system, CAP, that detects specific IgE to known allergens. The suspected allergen is bound to an insoluble material and the patient's serum is added. Any specific IgE in the serum binds to the material and can be identified by fluorescence-labelled anti-human IgE antibodies. It may provide additional evidence by indicating specific IgE sensitization but the sensitivity is disappointingly poor.

Case studies

The following cases are used to illustrate the investigative role of the allergy follow-up service.

Case study 1

A 49-yr-old female underwent an elective laparoscopic cholecystectomy. She had allergic rhinitis but was otherwise well. Her preoperative blood pressure (BP) was 140/80. One previous anaesthetic was uneventful. After 2 mg midazolam, 180 mg propofol, and 40 mg of rocuronium, she was intubated and volatile anaesthesia commenced. On transfer to theatre, she became flushed and tachycardic. Her airway pressure increased to >30 cmH₂O and BP decreased to 65/40. Anaphylaxis was suspected and was treated with two boluses of 100 µg of i.v. epinephrine, 2 litres of crystalloid, i.v. hydrocortisone 200 mg and chlorphenamine 10 mg. She recovered overnight in the critical care area and was referred for allergy testing (Table 1).

Allergy testing

Considerations

1. Neuromuscular blocking agents account for 60% of drug-related anaphylaxis. Succinylcholine carries the highest risk because of its molecular shape and size.
2. If clinical suspicion has been raised, all types of NMBAs should be tested by SPT ± IDT because of extensive cross-reactivity.

3. Cross-reactivity for NMBAs is as high as 65% on skin testing but the clinical response rate is much less. Eighty per cent of NMBA reactions occur without prior exposure.⁷

Future anaesthesia

Rocuronium and vecuronium are contraindicated. The negative intradermal testing to atracurium and succinylcholine does not guarantee their safety and therefore all relaxants must be avoided because of the incidence of cross-reactivity. If future NMBA use is clinically unavoidable, then a relaxant with negative SPT and IDT should be used (see Figs 1 and 2).

Case study 2

A 65-yr-old male had a central venous line inserted under local anaesthesia in theatre. He had no allergic history. Pre-insertion, the anaesthetist applied latex gloves, prepared the skin with alcoholic chlorhexidine, and injected 1% lidocaine. Immediately post central line insertion, the patient became flushed, developed a rash, abdominal pain, sweating, and felt unwell. He was immediately given hydrocortisone 100 mg and chlorphenamine 10 mg. The line was promptly replaced with a non-coated alternative (Table 2).

Allergy testing

Considerations

1. Chlorhexidine is a biguanide antiseptic found in a number of products. Routes of sensitization include mouthwash, ointments, *Instillagel*, and the coatings on some i.v. catheters.
2. Exposure can trigger significant reactions, potentially delayed if the chlorhexidine is absorbed gradually.
3. The allergic potential of chlorhexidine is under-recognized and may account for 27% of overlooked perioperative hypersensitivity reactions.⁸ It causes a spectrum of reactions from irritant dermatitis to a delayed IgE-mediated anaphylaxis.
4. Allowing chlorhexidine to dry before beginning a procedure may reduce the risk of reaction.

Future anaesthesia

Avoid chlorhexidine and use alternative antiseptics. Use chlorhexidine-free central lines and avoid *Instillagel*. The negative LA challenge ensured safe future use.

Table 1 Case study 1: MCT and skin testing

Test	Result	Drugs	Notes
MCT	Immediate 45 ng ml ⁻¹ Baseline 4 ng ml ⁻¹		(normal <14 ng ml ⁻¹)
SPT	Positive	Rocuronium	
	Equivocal	Vecuronium	
	Negative	Atracurium, succinylcholine, midazolam, propofol, latex, chlorhexidine	
IDT	Positive	Vecuronium	Rocuronium not performed as positive SPT
	Negative	Atracurium, succinylcholine, midazolam, propofol	



Fig 1 Skin prick testing showing the characteristic wheal and flare from a hypersensitivity reaction to rocuronium (Ro). Note: two places are tested on the forearm to improve detection rates. (Authors’ photograph.)



Fig 2 Further intradermal testing demonstrates a significant reaction to vecuronium (V). This is with a standard 1/10 dilution. (Authors’ photograph.)

Table 2 Case study 2: MCT and skin testing

Test	Result	Drugs	Notes
MCT	Immediate 18 ng ml ⁻¹ Baseline 3 ng ml ⁻¹		
SPT	Positive	Chlorhexidine	Neat and diluted
	Negative	1% lidocaine, latex	
IDT	Negative	1% lidocaine graded dilutions	Chlorhexidine not performed because of positive SPT
Challenge	Negative	s.c. 1% lidocaine	

Table 3 Case study 3: MCT and skin testing

Test	Result	Drugs	
MCT	Immediate 9 ng ml ⁻¹ Baseline 4 ng ml ⁻¹		
SPT	Negative	1% lidocaine 0.5% bupivacaine	
IDT	Negative	1% lidocaine 0.5% bupivacaine	1:1000, 1:100, 1:10 dilutions
Subcutaneous injections	Negative	1% lidocaine 0.5% bupivacaine	
	Positive	‘Lignospan Special’ dental cartridge	10 cm itchy, erythematous area

Case study 3

A 69-yr-old female was referred by a community dentist to exclude LA allergy. She had noticed episodes of dysphoria and palpitations during past dental treatments and developed urticaria on her forearm after hand surgery under LA using *Lignospan*. The patient was consented for LA challenging with i.v. access and vital signs monitoring (Table 3).

Allergy testing

Considerations

1. This female patient was successfully challenged to preservative free lidocaine and bupivacaine but demonstrated cutaneous allergy to the *Lignospan Special*. Many dentists prefer LA with vasopressor; however, this makes skin tests uninterpretable. Preparations include epinephrine (e.g. *Lignospan Special*), felypressin (e.g. *Citanest*), and also preservatives. In this case, sulphites in the *Lignospan* may have precipitated this reaction.
2. True type-1 hypersensitivity reactions to amide LAs are very rare but occur more frequently with esters. Type-4 hypersensitivity reactions are more common. Allergic reactions may be wrongly diagnosed after LA toxicity, psychological and vagal symptoms, sympathetic stimulation and reactions to additives. Rarely LAs may produce reproducible idiosyncratic reactions.

Future anaesthesia

The patient should receive preservative-free LA solutions, with or without epinephrine.

Case study 4

A 24-yr-old male underwent fixation of an ankle fracture. He had bronchial asthma needing occasional steroids but was otherwise well. There was a childhood history of penicillin-induced rash and vomiting.

Table 4 Case study 4: MCT and skin testing

Test	Result	Drugs	
MCT	Immediate 11 ng ml ⁻¹ 6 h 8 ng ml ⁻¹ Baseline 7 ng ml ⁻¹		Within normal range
SPT	Negative	Fentanyl, propofol, latex, teicoplanin 20 mg ml ⁻¹ , gentamicin 40 mg ml ⁻¹ , chlorhexidine 2%	
IDT	Positive	Teicoplanin	1/10 dilution
	Negative	Gentamicin (diluted and undiluted), propofol, fentanyl	1/10 dilutions

Anaesthesia was induced with fentanyl and propofol and a laryngeal mask airway inserted. He was transferred to theatre without complication. I.V. teicoplanin and gentamicin were administered. After 5 min he developed bronchospasm, and became profoundly hypoxic and hypotensive. No surgical stimulus had occurred. He was intubated and required 200 µg of i.v. epinephrine in three divided doses within 5 min before any improvement. Inhaled B₂ agonists, chlorphenamine 10 mg and hydrocortisone 100 mg, were given i.v. He was transferred ventilated, on an epinephrine infusion, to critical care and recovered overnight. Anaphylaxis was considered the most likely cause and he was referred for testing (Table 4).

Allergy testing

Considerations

Based on history, timing, and skin testing, teicoplanin appears to be the likely precipitant.

1. Despite positive IDT the SPT were negative. This implies that SPTs alone may fail to identify some drug allergies compared with the more sensitive IDTs.
2. After this life-threatening reaction, the MCT was normal.
3. The patient required multiple doses of epinephrine and an infusion.
4. Antibiotics account for 15% of anaesthetic anaphylaxis. This has increased with wider community exposure. Penicillins and β-lactams account for 70% of reactions and are typically IgE mediated. Similarity in the β-lactam ring side-chain morphology accounts for the cross reactivity. Third-generation cephalosporins have a markedly different arrangement and are less likely to cause anaphylaxis. Antibiotic allergy investigation is time consuming and requires SPT, IDT and where possible, identification of drug-specific IgE with supervised challenge testing, although not to teicoplanin in this case because of the risk of life-threatening anaphylaxis.

Future anaesthesia

There is a history of a potentially significant penicillin allergy so other β-lactam antibiotics should be avoided (carbapenems and cephalosporins). Teicoplanin is contraindicated. Microbiological advice should be sought for future antibiotic use.

Other precipitants

Latex

With greater recognition and adequate prevention strategies, latex reactions are on the decline. Reactions occur in two groups, those with significant previous exposure and those with an atopic predisposition. The prevalence of sensitization is 10% among healthcare workers and 15% in anaesthetic staff,⁹ but not all these individuals exhibit clinical allergy. Children undergoing repeated operations with high latex exposure or repeated bladder catheterization (e.g. spina bifida) have a 40–50% risk of sensitization. The clinical response can be delayed.

Opioids

Meperidine, codeine, and morphine are potent releasers of histamine and most reactions are mild and non-allergic involving pruritis and urticaria. IgE-mediated reactions can occur extremely rarely. Skin testing can be performed to fentanyl, alfentanil, and remifentanyl. Cross-reactivity can occur between morphine, codeine, and the other narcotics. A strong history should prompt avoidance of these agents.

Colloids

The mechanism is rarely IgE mediated and typically non-allergic. The older urea-linked gelatins (Haemacel) had greater allergenicity than modified fluid gelatins (Gelofusine). Reactions to HES are rare. If there is a known gelatine food allergy, related colloids should be avoided.

Hypnotics

Propofol allergy is uncommon and there is no evidence supporting soya or egg cross-reactivity. At high doses, propofol induces concentration-dependent histamine release and bronchospasm. The antigenic determinant is probably the isopropyl group and the reaction is best tested by IDT. Allergies to thiopental are very rare.

Dyes

Both *Patent Blue* alanine dye and *Isosulphan Blue* have been implicated with significant cross-reactivity and an anaphylactic incidence of 2–3%. The use of these dyes is increasing for lymphatic

mapping. Methylene blue may be used as an alternative but cross-reactivity can occur between the dyes.

Screening for anaphylaxis

There is no place for preoperative screening as the prevalence is too low. Previous exposure does not necessarily precede an allergic reaction. Although there is a known genetic predisposition to allergic disease, environmental exposure is more important.¹⁰ Therefore, testing patients based on family history of anaphylaxis to specific anaesthetic drugs is not indicated.

Future management of patients with previous anaphylaxis

Written information regarding the reaction, testing and advice for subsequent anaesthetic management should be available in the hospital notes and copied to the GP, patient, and clinicians involved. Patients should wear a warning bracelet or carry a card giving details of the allergy. The culprit agent may require reporting to the 'yellow card' system and AAGBI database. When anaesthesia is unavoidable after an unexplained or uninvestigated anaphylaxis, the case should be discussed with an expert centre and drugs with a low incidence of hypersensitivity used, such as volatile agents, benzodiazepines, and remifentanyl. Use of inhalation induction or regional anaesthesia should be considered. Avoid chlorhexidine and neuromuscular blocking agents (using remifentanyl) if safe to do so and ensure a latex-free environment. Pre-treatment with corticosteroids and antihistamines does not reliably prevent immune mediated reactions. Full monitoring should be applied and large-bore i.v. access established. The patient

should be fully pre-oxygenated. Vasopressors (particularly epinephrine) and full resuscitation facilities should be immediately available.

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Please see multiple choice questions 9–12.