

Review Article

Adverse drug reactions

K. Patton¹ and D. C. Borshoff²

1 Specialist Registrar, Department of Anaesthesia, University Hospital Bristol, Bristol, UK

2 Director, Department of Anaesthesia and Pain Medicine, St. John of God Murdoch Hospital, Perth, Western Australia

Summary

Adverse drug reactions are a cause of significant morbidity and mortality to patients and a source of financial burden to the healthcare system. Of the wide spectrum of adverse drug reactions, the most concerning to the anaesthetist remain anaphylaxis and malignant hyperthermia. Although the incidence of anaphylaxis under anaesthesia is difficult to ascertain, it occurs commonly enough that most anaesthetists will manage at least one case in their career. The wide range of drugs given in the peri-operative period and the variable presentation in the anaesthetised patient can delay diagnosis and treatment, and adversely affect outcome. Furthermore, despite improvements in testing, causative drugs can still be difficult to identify, as adverse reactions may be mediated by mechanisms other than IgE activation. With an increase in the reporting of anaphylaxis to newer anaesthetic drugs such as sugammadex, combined with change over the recent decades in the most likely causative peri-operative agents, it is imperative anaesthetists remain up to date on recent developments. In addition, they should be vigilant to patient characteristics, including pharmacogenetic variations that may predispose to adverse drug reactions, in order to help minimise risks of a reaction. The severity of adverse drug reactions to peri-operative drugs means morbidity and mortality remain high.

Correspondence to: K. Patton

Email: katiepatton57@gmail.com

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Anaesthetists are the medical specialists most likely to witness adverse drug reactions. This is due, in part, to the nature of the peri-operative period, in which patients are exposed to a large variety of potential allergens. These include anaesthetic drugs, antiseptics, dyes, contrast, latex and antibiotics.

Adverse drug reactions (ADR) are a source of significant morbidity and mortality, responsible for up to 6% of hospital admissions, carrying a mortality of 2% and costing the NHS £466 million per annum (£654 million, US\$ 602 million) [1]. They not only impact on the patient's quality of life, confidence in the healthcare system and length of hospital stay, but failure to identify ADRs can lead to unnecessary

investigations, potentially be detrimental to the patient and adding to the financial burden.

The incidence of adverse drug reactions to anaesthetic drugs is often quoted as between 1 in 10,000 and 1 in 20,000 [2]. However, it is likely these numbers are a gross underestimate. Differences in methodology between studies make it difficult to predict the true figure, but it may be somewhere nearer 1 in 3000 [3]. Despite comprehensive guidelines on recognition and management of adverse drug reactions, mortality from ADRs associated with anaesthesia is in the order of 10% [4].

Peri-operative anaphylaxis was the subject of the Royal College of Anaesthetists' 6th National Audit project, which aimed to establish the true incidence of

anaphylaxis in the UK, its epidemiology, short- and long-term outcomes, management, referrals, investigation and follow-up [5]. It is hoped that dissemination of these results will impact diagnosis and management of anaphylaxis in the same manner as previous audits have on awareness under anaesthesia and airway complications [6, 7]. It is a patient safety imperative that, as peri-operative specialists, we remain vigilant to the possibility of ADRs and be familiar with their recognition, immediate treatment and follow-up.

Definitions and classifications

Adverse drug reaction

The most commonly used definition of an ADR is a response to a drug that is ‘noxious, unintended and occurs at doses normally used in man’. This definition arose from the World Health Organization (WHO) report on International Drug Monitoring in 1972, and remains largely unchanged [8]. In contrast, the classification systems used and the nomenclature for allergy and anaphylaxis have changed considerably.

There are now two commonly used systems for classifying adverse drug reactions. The original classifications known as type A or augmented (dose-dependent and predictable) and type B or bizarre (dose-independent and unpredictable) are the best known and are often applied to reactions occurring in anaesthesia or intensive care. Types C–F have since been added (Table 1) [9]. In 2003, Aronson and Ferner observed that some adverse drug reactions do not always fit well into just one of these classes and proposed a system based on dose-relatedness, time-relatedness and susceptibility of the patient (DoTS) (Fig. 1) [10]. However, many of the drug reactions seen in anaesthetics and critical care still fit comfortably in the original type A and type B classification, and it remains simple to use and is familiar to clinicians. As such, it is still used by the Medicines and Healthcare products Regulatory Agency (MHRA) in its ADR collection process.

Anaphylaxis

In 2001, the European Academy of Allergy and Immunology (EAACI) redefined their nomenclature for allergy, including anaphylaxis. They defined anaphylaxis as a ‘severe, life-threatening generalised or

Table 1 Classification of adverse drug reactions. Adapted with permission [10].

Types of reaction	Features	Example
A – Augmented	Dose-related Common Related to known pharmacological effect	Hypotension with propofol
B – Bizarre	Predictable Non-dose-related Unpredictable Uncommon Not related to known pharmacological action of drug	Anaphylaxis Malignant hyperthermia Suxamethonium apnoea
C – Chronic	Dose-related Time-related Uncommon Related to cumulative dose	Propofol infusion syndrome
D – Delayed	Time-related Often dose-related Uncommon	Fluoride nephrotoxicity
E – End of use	Uncommon Occurs after withdrawal of drug	Rebound hypertension following cessation of clonidine infusion
F – Failure	Dose-related Uncommon May be caused by drug interactions	Failure of oral contraceptive pill with sugammadex use

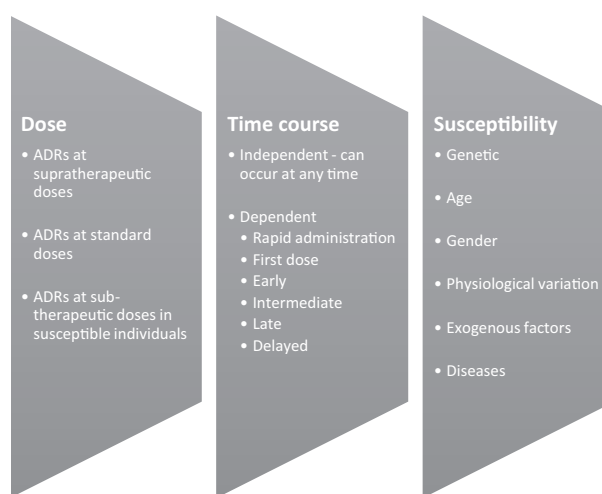


Figure 1 Dose-relatedness, time-relatedness and susceptibility of the patient (DoTS) classification [10]. ADR, adverse drug reaction.

systemic hypersensitivity reaction'. It can be subdivided into allergic or non-allergic anaphylaxis, with allergic anaphylaxis further subdivided into IgE-mediated and non-IgE-mediated. The term anaphylactoid is now obsolete, and all non-immune-mediated reactions should be referred to as non-allergic anaphylaxis [11]. This new nomenclature highlights difficulties in identifying potential anaphylaxis triggers, as skin prick testing will only identify IgE-mediated reactions, and attributing causality may require additional investigations such as intradermal testing, which carries the risk of precipitating further anaphylaxis [12]. In addition to drugs which cause ADRs by IgE or non-IgE-mediated mechanisms, there are others, such as non-steroidal anti-inflammatory drugs (NSAID) and neuromuscular blocking (NMB) agents, that can cause a reaction by both mechanisms, further complicating diagnosis (Table 2) [13].

Factors contributing to adverse drug reactions

Patient characteristics

Age

The physiological differences in children and the elderly make them more susceptible to ADRs. Differences in renal, hepatic and cardiovascular systems all increase the chance of an ADR [14].

Polypharmacy

This increases the chance of an ADR secondary to drug interactions. Polypharmacy can also alter

pharmacokinetics, and the underlying disease may affect pharmacodynamics [15, 16].

Sex

Some drugs cause anaphylaxis more commonly in females; these include NMBs and latex. Females are almost twice as likely to experience an ADR. This may be attributable to pharmacokinetic differences related to body mass, hepatic clearance and hormones [17].

Smoking

Anaphylaxis to antibiotics occurs more frequently in smokers and could result from sensitisation due to repeated courses for respiratory infections [18].

Atopy

Latex allergy and anaphylaxis to contrast media are more common in patients with a history of atopy. They are also more common in patients with an allergy to fruits, especially banana, chestnut and avocado [19].

Previous exposure

Healthcare professionals and patients undergoing multiple procedures, such as those with spina bífida, are at increased risk of latex allergy. This also applies to workers who have an occupational exposure to latex [18, 19]. However, unlike those high-risk patients where environmental sensitisation from a young age is the primary mechanism, there may be a genetic component predisposing healthcare workers in addition to prior exposure [20].

Possible environmental sensitising agents

There is considerable variation between countries in the incidence of anaphylaxis, particularly to NMBs. Although variations in reporting rates may account for some of this difference, it may be that environmental factors are involved. For example, many common chemicals found in domestic products contain allergenic epitopes similar to the quaternary ammonium ions thought to be responsible for adverse reactions to the NMBs [21]. The most well-known is the IgE sensitisation of patients to NMBs, particularly suxamethonium, from the use of pholcodine, a historical component of a popular cough medicine in Europe.

Table 2 Mechanism causing hypersensitivity reactions for drugs commonly used in the peri-operative period.

IgE-mediated allergy	Non-allergic drug hypersensitivity
NSAID	NSAID
Antibiotics	Opioids
Latex	Hypnotics
NMB	NMB
Heparin	Contrast media
Contrast media	
Dyes, e.g. patent blue	
Disinfectants	
Hypnotics	

NSAID, non-steroidal anti-inflammatory drug; NMB, neuromuscular blocking agent.

The discrepancy between rates of anaphylaxis to NMBs between Scandinavian countries prompted a search for an environmental factor. The rate of reported anaphylaxis to NMBs dramatically reduced in Sweden since the withdrawal of pholcodine in the 1980s, and a recent review in Norway shows similar results since its withdrawal in 2007 [22]. A similar theory is postulated for the increasing amount of anaphylaxis seen to sugammadex, based on our ingestion of up to 4 g of cyclodextrins a day [23].

Pharmacogenetics

Differences in pharmacogenetic diversity can help explain the differences seen in both pharmacokinetics and efficacy of many drugs used in the peri-operative period, including the varied responses to commonly used anaesthetic drugs such as propofol, fentanyl and ondansetron [24–26]. Genetic predispositions of particular relevance in anaesthesia include: suxamethonium apnoea; malignant hyperthermia; acute porphyria; and ADRs secondary to variations of the cytochrome P450 system (Table 3) [27]. With the cost of gene sequencing likely to fall, the pre-emptive identification of those of risk of ADRs secondary to pharmacogenetics may become an option. However, although this would allow for individually tailored peri-operative care, it raises practical, ethical and financial considerations.

Immune response

An immunological response, usually involving in the formation of antibodies, can lead to hypersensitivity

reactions. These can be classified into four main types (Table 4).

The ADRs of greatest significance to the anaesthetist in the peri-operative period are undoubtedly anaphylaxis and malignant hyperthermia. Much of the remainder of this article focusses on the recognition, management and investigation of these reactions. Management of other ADRs largely relies on avoidance of known precipitants and knowledge of any genetic predisposition likely to cause problems.

Recognition of hypersensitivity reactions

The first step to managing an adverse drug reaction is identifying it. This may not be straightforward in an anaesthetic setting. Simultaneous exposures to multiple potential allergens and the physiological effects of anaesthesia can muddy the waters. For example, although bronchospasm may be due to an ADR, it could simply be the response to irritation by a tracheal tube. As well as intravenous (i.v.) triggers, there are ‘hidden’ drugs such as latex and chlorhexidine to consider, so identification of the precipitant may not be possible at the time of reaction [2]. Peri-operative reactions can be severe or life-threatening, with the potential for a more severe reaction on repeated exposure to the allergen, making identification of the responsible agent extremely important for future avoidance.

Clinical presentation can vary from skin and temperature changes to life-threatening cardiovascular collapse. Physiological changes related to anaesthesia or

Table 3 Genetic variations with relevance to anaesthesia.

Genetic variation	Effect	Related drugs
Plasma pseudocholinesterase	Deficient enzyme activity, prolonged drug effect (suxamethonium apnoea)	Suxamethonium, mivacurium
Defective coding for ryanodine receptor	Malignant hyperthermia	Inhalational anaesthetics Suxamethonium
CYP2D6 gene	Poor, intermediate, extensive or ultrarapid metabolisers	Diazepam Codeine Tramadol Ondansetron
Porphobilinogen deaminase deficiency	Acute intermittent porphyria	β-blockers Barbiturates Clonidine Cephalosporins Benzodiazepines Phenytoin

Table 4 Types of hypersensitivity reactions.

	Mechanism	Example
Type I	Immediate	Anaphylaxis, angio-oedema
Type II	Cytotoxic	Transfusion reaction
Type III	Immune complex-mediated	Reactive arthritis
Type IV	Delayed, cell-mediated	Contact dermatitis

critical illness can delay recognition. The following is a brief guide, highlighting the wide variation in presentation that makes prompt recognition challenging. The commonest presentations of anaphylaxis under anaesthesia can be found in Table 5 [17, 28].

Skin changes

These may be absent, hidden under drapes or coloured antiseptic or only appear in cases of profound circulatory collapse once perfusion has improved [2]. If the patient is on high-dose corticosteroids or antihistamines, skin changes may be masked. Patients with urticaria should be referred for investigation, but localised and transient rashes caused by local histamine release are unlikely to represent significant hypersensitivity. In particular, transient flushes or rashes secondary to known histamine-releasing drugs, such as NMBs and opioids, usually resolve spontaneously and do not warrant specific investigation [29].

Airway

Bronchospasm as an isolated phenomenon may not be allergic in nature but a result of pre-existing disease such as asthma or due to inadequate depth of anaesthesia. When patients' lungs are mechanically ventilated, bronchospasm may present as a prolonged expiratory phase, high airway pressures, decrease in

oxygen saturation or audible wheeze/rhonchi on auscultation [2].

Cardiovascular changes

Tachycardia may not always be present, or may be masked in patients on beta-blockers.

In contrast, hypotension may commonly present as the only symptom, and can be prolonged and resistant to treatment with the usual vasopressors [2]. When there is significant hypotension associated with anaphylaxis, there is likely to be a significant increase in serum tryptase [30]. All cases of prolonged or difficult-to-treat hypotension in the peri-operative period should be considered for allergy investigation.

It is important to consider all sources of a patient's exposure to allergens in the peri-operative period when referring patients. This should include all drugs (i.v. and oral), disinfectants, dyes, transfusions and the use of medicines containing polyethylene glycols and methylcellulose, such as pre-operative laxatives. The substances which cause anaphylaxis most commonly in the peri-operative period are listed in Table 6 [31].

Of interest is the addition to this list of patent blue dye. In recent years, there has been an increase in the number of cases of severe anaphylaxis reported it being commonly used for sentinel node mapping in breast surgery [32]. One multi-centre study put the incidence at 1:3000, considerably higher than other drugs administered in the peri-operative period [33]. This has led to the suggestion that pre-operative skin testing should be conducted before its use [34]. However, due to intradermal administration and cutaneous uptake, ADRs to patent blue dye often appear 15-30 min after injection and may produce prolonged, biphasic reactions resistant to treatment [35].

In all cases of suspected ADRs, careful documentation is essential, with attention to the timing of symptoms

Table 5 Presentations of anaphylaxis under anaesthesia.

Cardiovascular	75-88%
Hypotension	18%
Cardiovascular collapse	50%
Cardiac arrest	6%
Bradycardia	2%
Bronchospasm	36-40%
Cutaneous signs	45-90%
Angio-oedema	7-25%

Table 6 Agents most commonly responsible for hypersensitivity reactions in anaesthetic practice.

Neuromuscular blocking agents	38%
Antibiotics	31%
Chlorhexidine	18%
Patent blue dye	7%
Latex	6%
Opioids	2%
Local anaesthetics	2%

following drug administration or exposure to potential triggers. The possibility of missed allergens should be considered in patients before further differential diagnoses are considered. Such differentials may include an undiagnosed mast cell disorder, which can also present with severe hypotension triggered by pain, stress and extremes of temperature in the peri-operative setting [36].

Management of adverse drug reactions

It is beyond the scope of this article to review the management of adverse drug reactions for each individual class. Detailed guidelines on the management of anaphylaxis and malignant hyperthermia can be found on the AAGBI website (<https://www.aagbi.org>). In broad terms, less severe ADRs may be managed by lowering the dose or ceasing the drug, and providing supportive therapy.

Rocuronium and sugammadex

Much interest has been generated in the possibility of using sugammadex, in addition to standard management strategies, for the treatment of rocuronium-induced anaphylaxis. This arose from the hypothesis that the cyclodextrin sugammadex encapsulates rocuronium and therefore prevents the allergenic groups of rocuronium from interacting with IgE, mast cells and basophils [37]. Molecular models and in vivo experiments, however, do not support this theory [38]. Sugammadex has itself been shown to cause anaphylaxis [23, 39] and is not currently recommended in the treatment of rocuronium-induced anaphylaxis [40].

Reporting of adverse drug reactions

In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) mediates the monitoring of adverse drug reactions through the yellow card scheme [41]. This has been in place for healthcare professionals since the thalidomide disaster in 1964. In 2003, the MHRA took primary responsibility for the collection and analysis of ADRs, and from October 2005, the scheme became accessible to both the general public and patients. Yellow cards can be found in the British National Formulary (BNF), Monthly Index of Medical Specialities (MIMS) and the Association of the British Pharmaceutical Industry (ABPI) Medicines

Compendium. They can also be completed online at <https://yellowcard.mhra.gov.uk>.

For drugs that are well established, only serious adverse effects should be reported (Table 7). For newer drugs, or those under additional surveillance, an inverted black triangle (▼) will appear in the product information, advertising material and the drug entry in the BNF, MIMS and ABPI Medicines Compendium. For these drugs, all ADRs should be reported, however minor (Table 7) [42].

Many countries have comparable pharmaco-vigilance centres collecting data on ADRs and there are now 125 members of the WHO Programme for International Drug Monitoring. This information is collated by the ADR monitoring centre in Sweden and used to identify the first signs of danger posed by a drug. It was established in 1978 as a response to the global thalidomide disaster, and continues to have a significant role in the development of systems for drug safety worldwide [43].

For anaphylaxis, the anaesthetist who gave the anaesthetic, or the supervising consultant anaesthetist, is responsible for ensuring that the reaction is investigated. The patient should be referred to a specialist allergy or immunology centre. A list of centres can be found on the AAGBI (<https://www.aagbi.org/safety/allergies-and-anaphylaxis>) or British Society for Allergy and Clinical Immunology (<http://www.bsaci.org/find-a-clinic/index.htm>) websites.

Reactions should be notified to the AAGBI National Anaesthetic Anaphylaxis Database via an allergy referral (<https://www.aagbi.org/safety/allergies-and-anaphylaxis>). The patient, surgeon and general practitioner should all be informed. Once the patient has been investigated and the causative agent determined, a yellow card should be completed [18]. The Yorkshire Allergy Pack can also be

Table 7 Adverse effects of well-established drugs to report to the Medicines and Healthcare products Regulatory Agency (MHRA).

Serious adverse effects

Fatal
Life-threatening
Disabling or incapacitating
Congenital abnormalities
Involved or prolonged hospitalisation
Medically significant

downloaded from the AAGBI website containing all the relevant forms and a useful checklist for the referral process.

Malignant Hyperthermia assessment and monitoring is coordinated in the UK by a central unit at St James's Hospital In Leeds [44]. In addition to their screening service, they operate a 24-h hotline for medical practitioners, providing guidelines for referral criteria. Perhaps unsurprisingly, up to 50% of referrals can be attributed to other causes. The malignant hyperthermia unit also maintains a national registry of cases and genetically predisposed families. Such a registry helps provide advice on risk assessment to affected families and their relatives.

Investigations of adverse drug reactions

Those reactions referred for investigation from the peri-operative period are likely to be type B (hypersensitivity type-1 or anaphylaxis). About 60–70% of these reactions during anaesthesia are mediated by IgE, with more than 7000 cases published in the last 25 years [45]. It is important to have a systematic approach to the investigation of ADRs, and it requires a specialist allergist.

Serum tryptase

Tryptase is a peptidase made and stored in mast cells. It can be found in two forms, alpha and beta. Alpha tryptase is released constantly at low levels, but raised baseline levels can be found in systemic mastocytosis [46]. Symptoms of a hypersensitivity reaction and the presence of a raised beta serum tryptase increase the probability of anaphylaxis, but normal levels do not exclude it. As people have varying baseline levels of serum tryptase, it is important to collect more than one sample so comparisons can be made. In some individuals, it can take more than 24 h following a reaction for baseline levels to return to normal, and so a control sample should be taken after this time. There are timing guidelines for taking levels in the UK (Table 8) [18, 28, 47]. A significant increase in the concentration of serum tryptase ($> 50 \mu\text{g.l}^{-1}$) suggests an IgE-mediated anaphylaxis [48]. Non-IgE-mediated reactions (such as complement-mediated reactions) may generate lower concentrations of $20\text{--}50 \mu\text{g.l}^{-1}$ [48]. Increased basal tryptase levels may be found in

patients with systemic mastocytosis, mast cell activation syndrome or haematological diseases such as myelodysplastic syndromes and mast cell leukaemia [48]. These may or may not be known about before investigation and may complicate diagnosis.

Skin testing

This takes the form of both skin prick testing and intradermal testing. These can be performed as soon as a patient has made a full recovery. Skin prick testing involves placing a drop of the drug on the volar surface of the forearm and pricking the skin through the drop with a lancet. The results are read after 15–20 min with histamine and saline solutions used as positive and negative controls. Drugs with antihistamine activity should be therefore discontinued several days before testing, but steroids (oral or inhaled) do not need to be stopped. Intradermal tests are usually performed on the forearm or back when skin prick tests are negative. They are more difficult to interpret with a higher false-positive rate and are more likely to precipitate a systematic reaction [18]. The European Network for Drug Allergy (ENDA) has published a list of non-irritant dilutions for skin prick and intradermal testing. It is notable that skin tests are not useful for non-IgE-mediated reactions, such as those caused by contrast media or NSAIDs [49]. As previously mentioned, anaesthetic drugs can cause IgE- or non-IgE-mediated reactions, with some causing anaphylaxis through either mechanism, adding to the difficulty in agent identification [13].

IgE assays

There are IgE assays available for a limited number of drugs, including chlorhexidine, succinylcholine, latex and penicillin, but their sensitivity and specificity is variable. The presence of IgE is not necessarily proof

Table 8 Timings for serum tryptase sampling following suspected anaphylaxis.

	Timing
Sample 1	As soon as possible but do not delay resuscitation to take sample
Sample 2	1–2 h after onset of symptoms
Sample 3	24 h after onset of symptoms or in follow-up clinic (to measure baseline tryptase)

the agent is the cause of a reaction, but indicates the individual has an allergic sensitization. However it does provide a possible mechanism if there is correlation with other clinical and laboratory information. The availability of these tests is variable depending on the country and speciality of the laboratory [18, 45].

Basophil activation test

As well as mast cell activation, allergens stimulate histamine release and basophil surface activation of CD63 and CD203. The basophil activation test and histamine release test are not currently widely available to clinicians, but may be useful where hypersensitivity is highly suspected but not supported by skin testing or IgE assays. [2, 18].

Challenge testing

In instances where skin tests are not diagnostic (such as NSAIDs and opiates) or where there is a clinical need to use a drug suspected of causing an ADR in the future, drug challenging may be considered. This should only be undertaken in a specialised centre given the risk of precipitating anaphylaxis. Patients should be consented, fully monitored and have i.v. access before a graded exposure to the drug orally, subcutaneously or intravenously [45].

Conclusion

Adverse drug reactions, particularly those in the perioperative period, can be severe and life-threatening. They impact on patient stay, healthcare costs, morbidity and mortality, and potentially affect future anaesthesia or drug exposure. Recognition of an ADR and identification of the causative agent can be challenging. As peri-operative specialists, anaesthetists must remain up to date with all aspects of ADRs, including possible clinical presentations, common causative agents, appropriate management and subsequent reporting.

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