Abstract

This article describes the signs and symptoms of drug allergy, and explains the effects that it can have on patient care. It outlines the risk factors for the development of drug allergy, along with the mechanisms by which allergic reactions are mediated. This article also explains the tests used to diagnose drug allergy, and provides recommendations for the management of patients who experience an allergic reaction to a drug. The author uses case studies to emphasise the importance of the role of the nurse in managing, reporting and documenting drug allergies appropriately.

Identification and management of drug allergy

Kathryn Powrie

Immediate hypersensitivity can occur when a person’s immune system reacts abnormally to a substance that is usually harmless, known as an allergen. Previous exposure to an allergen causes sensitisation in certain individuals, resulting in the immune system producing immunoglobulin E (IgE) antibodies in response to the allergen. When the individual is re-exposed to the allergen, it binds to IgE on the surface of mast cells, which cause these cells to degranulate, releasing histamine and other pro-inflammatory chemical mediators (Gell and Coombs 1975). Anaphylaxis to penicillin is an example of this phenomenon.

Drug allergy is one type of adverse drug reaction (ADR), which patients may experience when taking a medicine, whether this is purchased over the counter or prescribed. Edwards and Aronson (2000) defined an ADR as ‘an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product’. The term ADR covers a variety of reactions, including drug overdose, side effects and drug interactions, which can occur in anyone taking a particular drug and are largely predictable. In contrast, drug allergy is an ADR with an established immunologically-mediated mechanism, which occurs only in susceptible individuals (Mirakian et al 2009).

There are four types of allergic reaction, which are classified using the Gell and Coombs (1975) system and are shown in Table 1. Many patients and healthcare professionals mistake other types of ADRs for drug allergies, which can mean that patients are inappropriately labelled as allergic.

Incidence and effects of drug allergy

Determining the incidence of drug allergy is challenging because most of the available data is related to ADRs as a group rather than drug allergy specifically (Demoly 1999, Pirmohamed et al 2004, Thong and Tan 2011). International studies on ADRs have tended to focus on specific clinical areas such as emergency department admissions, outpatients or hospital inpatients, and most have studied cutaneous ADR (a drug reaction affecting the structure or function of the skin, its

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Correspondence

Kathryn.Powrie@meht.nhs.uk

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appendages or mucous membranes) without considering drug allergy separately (Pirmohamed et al 2004, Gibbison et al 2012).

Pumphrey and Robert’s (2000) UK study of 56 postmortem following fatal anaphylaxis found that 37.5% (n=21) of deaths were caused by drugs or medicinal products such as contrast media. Furthermore, drug allergies and ADRs account for 62,000 admissions to hospital annually in England and there is evidence that the number of reactions is increasing (National Institute for Health and Care Excellence (NICE) 2014). A UK analysis of patient safety incidents reported between 2005 and 2013 found 18,079 incidents relating to drug allergy. Of these incidents, six were deaths and 19 were rated as causing severe harm. Significantly, a total of 13,071 (72%) of these patient safety incidents were ‘near-misses’ in which a drug had been prescribed, administered or dispensed to a patient who was known to have an allergy to that drug (NICE 2014).

It has been estimated that 10-15% of hospital inpatients will experience an ADR, and a proportion of these will be drug allergies (Thong and Tan 2011). In addition to the risk of causing death, drug allergy also significantly affects patient morbidity and may prolong hospital stays (Thong and Tan 2011). This may be because standard treatment cannot be used, resulting in possible delays to treatment, use of less effective treatments such as second-line antibiotic therapy, and the repeated use of general anaesthetics for dental treatment if local anaesthetic allergy is suspected (Mirakian et al 2015). As such, drug allergy represents a clinical burden to patients and a financial burden to healthcare organisations as a result of additional drug costs and increased bed days (Demoly et al 1999).

Role of the nurse in drug allergy
The nurse’s role in relation to drug allergy is multifaceted. All nurses are responsible for the safe administration of medicines and are often the healthcare professionals to whom patients will present first with symptoms. Standard 8 of the Nursing and Midwifery Council (NMC) (2007) Standards for Medicines Management states that nurses must check if the patient has any known drug allergies before administering a medicine, and must manage, document and report any ADRs that occur without delay. In addition, many nurses are now non-medical prescribers, and as such it is important that they understand the potential for ADRs and allergic reactions, how to manage them and which patients to refer to an allergy service for specialist investigation.

Risk factors
Research suggests that some patients are at increased risk of developing drug allergy; for example, women are more likely than men to experience ADRs (Vervolet and Durham 1998, Mirakian et al 2009). Repeated exposure to a drug is an important factor, because the rate of ADRs rises in patients who are frequently prescribed the same drugs or chemically similar drugs (Mirakian et al 2009).

Key points
- Pumphrey and Robert’s (2000) UK study of 56 postmortems following fatal anaphylaxis found that 37.5% (n=21) of deaths were caused by drugs or medicinal products such as contrast media.
- Drug allergy represents a clinical burden to patients and a financial burden to healthcare organisations as a result of additional drug costs and increased bed days (Demoly et al 1999).
- The treatment of an allergic reaction depends on its severity, and all such reactions should be assessed systematically using the ABCDE (assessment, breathing, circulation, disability and exposure) approach.
- Managing drug allergy consists of both diagnosis and avoidance of the culprit drug. However, management may also require avoidance of chemically similar drugs and identification of suitable alternatives (Mirakian et al 2009, Ewan et al 2010, Odedra and Farooque 2014).

### TABLE I. Types of allergic reaction

<table>
<thead>
<tr>
<th>Type</th>
<th>Immune mediators</th>
<th>Mechanism</th>
<th>Clinical features</th>
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| Type I | Immunoglobulin E (IgE) mediated – immediate hypersensitivity | Allergen (drug) binds to IgE on the surface of mast cells, causing the rupture and release of histamine and other pro-inflammatory mediators | » Urticaria  
» Angioedema  
» Exacerbation of asthma  
» Symptoms with respiratory or cardiovascular compromise |
| Type II | Immunoglobulin G (IgG) and/or immunoglobulin M (IgM) mediated – cytotoxic reaction | Caused by IgG or IgM reacting to antibodies on the cell membrane, causing cell lysis | » Haemolytic anaemia |
| Type III | IgG and/or IgM mediated – immune complexes | Immune complexes form when IgG and IgM bind to the circulating allergen. These complexes are deposited in tissues, causing cell death | » Vasculitis  
» Lymphadenopathy  
» Serum sickness |
| Type IV | T cell mediated – delayed hypersensitivity | Occurs when a sensitised T cell is re-exposed to, and combines with, the allergen. This causes release of pro-inflammatory mediators, resulting in symptoms 24-48 hours after exposure | » Contact dermatis  
» Stevens-Johnson syndrome  
» Drug rash with eosinophilia and systemic symptoms (DRESS)  
» Acute generalised exanthematous pustulosis (AGEP) |

(Gell and Coombs 1975, Mirakian et al 2009, National Institute for Health and Care Excellence 2014)
Underlying disease can also increase the risk of drug allergy; for example, patients who have human immunodeficiency virus are increasingly likely to experience allergic reactions as a result of changes in their immune system (Mirakian et al 2009). Underlying atopic diseases, such as asthma, eczema and hay fever, do not predispose patients to drug allergy. However, if a patient who has asthma experiences an allergic reaction, it is likely to be more severe because of the resultant airway compromise (Mirakian et al 2009, Thong and Tan 2011, NICE 2014).

Signs and symptoms

Allergic reactions to drugs can be divided into three main groups: immediate, non-immediate and non-immediate with systemic involvement. These groups each have varying signs and symptoms and occur within differing time frames (Pumphrey 2000, Mirakian et al 2009).

Immediate reactions usually occur within one hour of exposure to the drug, but can occur as quickly as one minute following the administration of IV drugs. Symptoms can range from urticaria (hives) (Figure 1) and angioedema (Figure 2) to life-threatening anaphylaxis, in which skin symptoms are combined with hypotension or bronchospasm. Anaphylaxis during general anaesthesia can be challenging to recognise because skin symptoms are often unseen because the patient is covered (NICE 2014).

Non-immediate reactions are subdivided into those with and without systemic involvement. Reactions without systemic features typically comprise widespread macules and/or papules or a fixed drug eruption – indicated by a red circular mark occurring in the same place each time the drug is taken (Figure 3) – and usually occur 3-10 days after exposure (Mirakian et al 2009, NICE 2014).

Non-immediate reactions with systemic involvement can be severe. The first type of reaction is drug rash with eosinophilia and systemic symptoms (DRESS), whose features include widespread red macules and/or papules, erythroderma, fever, lymphadenopathy and liver dysfunction. The second type is Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis, which cover a spectrum of severity. Often the skin rash is preceded by a sore throat or cough. The rash spreads to form widespread erythematous lesions, with blistering and mucosal and epidermal detachment, as well as ocular involvement, such as corneal damage affecting vision (Basu et al 2018). SJS affects 10-30% of the body surface area, whereas toxic epidermal necrolysis affects more than 30% of the body surface area and is associated with significant mortality (Mirakian et al 2009). SJS and toxic epidermal necrolysis may occur between three days and six weeks after exposure (NICE 2014).

Treatment of allergic reactions

The treatment of an allergic reaction depends on its severity, and all such reactions should be assessed systematically using the ABCDE (assessment, breathing, circulation, disability and exposure) approach. Initially, the suspected drug should be stopped immediately. First-line treatment for anaphylaxis is intramuscular adrenaline (epinephrine), followed by supportive treatment, which may include antihistamines, corticosteroids, IV fluids, bronchodilators and high-flow oxygen (Resuscitation Council (UK) (RCUK) 2012). DRESS, SJS and toxic epidermal necrolysis are severe reactions that require hospitalisation, and initial treatment is similar to the care of patients with burns, comprising fluid replacement, wound care and pain relief.

In the acute setting, serial measurement of the patient’s serum tryptase level can be beneficial. Tryptase is a marker of mast cell degranulation and can be useful in diagnosing anaphylaxis. A clotted blood sample should be collected as soon as possible after the reaction, and at two hours, and a baseline sample should be collected at more than 24 hours after the reaction (Vervolet and Durham 1998, Mirakian et al 2009, NICE 2014).
Documenting a suspected drug allergy

Patients who have an allergic reaction to a drug may present initially to a practice nurse, or a staff nurse if they are an inpatient. Consequently, nurses are well placed to undertake and document an initial assessment of the patient. NICE (2014) guidelines set out the main points that should be documented when recording a suspected drug allergy, including:

- Generic and proprietary name of the drug, since some excipients (pharmacologically inactive ingredients added to medicines as binding agents, dyes or preservatives) have been recognised as causes of allergic reactions, for example polyethylene glycol.
- Drug dose.
- Indication for the drug’s initial prescription.
- Date and time of the allergic reaction.
- Description of the allergic reaction.
- Route by which the drug was administered.
- Number of doses or days the drug had been taken for before the allergic reaction occurred.

NICE (2014) guidelines recommend that drug allergy is recorded in one of the following ways:

- None known.
- Unable to ascertain.
- Allergic to drug X, with a record of the date of reaction and symptoms experienced by the patient. The use of ‘unable to ascertain’ reduces the risk of a known drug allergy being missed in patients who have been admitted as an emergency and may be unable to provide a clear history at presentation, for example because they are confused or unconscious. It acts as a prompt to question the patient again regarding their allergy status where possible, and to update their records accordingly. One ongoing issue in healthcare services is the use of various computer systems, which might not be adequately linked and thus do not share all of the necessary data. This is a risk because drug allergies may not always be transcribed onto all of the relevant computer systems.

Once a diagnosis of drug allergy has been made, this should be clearly documented in written and electronic notes and drug charts, and communicated with anyone else involved in the patient’s care, for example their dentist.

Referral for specialist investigation

Given the large number of patients who report a drug allergy, it would not be possible to undertake testing for all of them. Instead, referral to an allergy service for specialist investigation should be targeted at certain individuals. For instance, with a penicillin allergy, specialist investigation would be targeted at those who (Mirakian et al 2009, NICE 2014):

- Had a reaction under general anaesthetic where penicillin was given.
- Report allergy to penicillin and one other class of antibiotics.
- Have an infection that requires penicillin, for example recurrent urinary tract infections (UTIs) or neurosyphilis.

Referral for specialist investigation is also recommended for all reactions during general anaesthesia, suspected drug-related anaphylaxis, suspected local anaesthetic allergy and all severe non-immediate reactions. In addition, a specialist opinion should be sought if suspicion of drug allergy is compromising patient care.

Testing and diagnosis

Diagnosing drug allergy can be complex because not all of its mechanisms are fully understood. When investigating a suspected drug allergy, the nurse should begin by taking the patient’s history and checking all available documentation relating to the incident. It is often necessary to review the patient’s medical and nursing records, and anaesthetic and drug charts, because allergens may not be immediately obvious (Adkinson 1984, Mirakian et al 2009, RCUK 2012).

Skin rash is often challenging to describe and photographs taken by the patient can be useful in the diagnostic process. Following this, the patient may require a series of tests. It is important that the risks of testing do not outweigh the benefits of a diagnosis, and this should be carefully considered for each individual patient. Depending on the suspected mechanism, testing may include blood tests to identify IgE antibodies, skin prick and intradermal tests with diluted concentrations of the drug or drugs and, if these tests are negative, a supervised, staged challenge (where a drug is administered in stages to test if it causes a reaction) (Adkinson 1984, Mirakian et al 2009, Ewan et al 2010, RCUK 2012, Odedra and Farooque 2014). However, since blood tests for drug allergy are limited, further investigation is often required.

Skin prick (Figure 4) and intradermal tests (Figure 5) must be undertaken with non-irritant concentrations of the drug in a sequential manner, starting with the lowest concentration. This often requires the drug to be diluted several times, and the non-irritant concentration strength can vary considerably from drug to drug.
Case study 1 – penicillin allergy
Alison is a 63-year-old woman with a history of penicillin allergy dating back to childhood. Details of her reaction to penicillin are unclear and she has avoided taking it for several years. At present, she is experiencing recurrent urinary tract infections (UTIs), which have become resistant to other antibiotics but are sensitive to amoxicillin.

This case study demonstrates that some patients may have a vague history of an allergic reaction to a drug dating back several years and for which documentation is not available. This is commonly seen with reported penicillin allergy.

In total, 10% of the adult UK population self-report penicillin allergy; however, when provocation testing is undertaken, 90% of these patients do not react to the drug (National Institute for Health and Care Excellence 2014, Mirakian et al 2015). Therefore, when encountering a patient who has a possible history of drug allergy or has had an allergic reaction, the nurse has to decide whether referral to an allergy service for specialist investigation is required, or if the drug should be avoided as a pragmatic measure.

In this case study, Alison underwent a series of investigations, commencing with blood tests to identify immunoglobulin E antibodies to penicillin V, penicillin G and amoxicillin. This was followed by skin prick testing with diluted concentrations of penicillin major and minor determinants (representing different parts of the penicillin structure) and amoxicillin. The same solutions were used for intradermal testing. Finally, Alison underwent a staged oral challenge with amoxicillin syrup over a four-hour observed period, and was discharged with a five-day course of amoxicillin to take at home.

A positive test at any stage would confirm drug allergy and the testing would be halted. Alison completed all stages of the testing without experiencing any adverse reactions and has since been able to take penicillin for a UTI.

Case study 2 – anaphylaxis during general anaesthesia
Sue is a 45-year-old woman who underwent a mastectomy for breast cancer under general anaesthetic and developed anaphylaxis intraoperatively. During the operation, she was noted to be hypotensive (50/30mmHg) and tachycardic with a generalised red rash.

Following resuscitation with adrenaline (epinephrine), fluids, corticosteroids and antihistamines, Sue’s mastectomy was completed, but her breast reconstruction was not undertaken.

Tryptase levels taken during the surgery were raised at 46ng/L (normal range: 0–4ng/L), providing evidence of mast cell degranulation.

Subsequent review of Sue’s anaesthetic and drug charts demonstrated that the drugs she was given were propofol, remifentanil, midazolam, co-amoxiclav (amoxicillin and clavulanic acid) and rocuronium bromide, in addition to exposure to latex and chlorhexidine used in skin preparation.

Identifying the culprit drug responsible for allergic reactions occurring during general anaesthesia presents a particular challenge because many drugs can be administered during a short time frame.

The timing of the reaction may indicate which drug is the likely culprit; however, all drugs administered must be tested and excluded as a cause (Adkinson 1984).

In this case study, the testing involved blood tests for allergic antibodies to penicillin, latex and chlorhexidine, followed by skin prick tests with diluted concentrations of each of the drugs and substances used during surgery.

The test for rocuronium, a muscle relaxant, was positive. However, to exclude the other drugs, intradermal testing was undertaken using non-irritant dilutions.

If a muscle relaxant is found to be the cause of an allergic reaction, it is also necessary to test all alternative muscle relaxants because there is significant cross-reactivity between these drugs resulting from commonalities in their chemical structure, which could cause a further reaction if used in future surgery (Adkinson 1984, Odedra and Faroque 2014).

One Australian study found that 65% (28/43) of patients who had a positive test to rocuronium had evidence of cross-reactivity to other muscle-relaxing agents (Breereton and Russell 2012).

The testing in Sue’s case found evidence of cross-reactivity with suxamethonium chloride, which was identified through a positive intradermal test. The final stage of testing was an oral challenge with co-amoxiclav, which was negative.

The patient was advised that rocuronium was the cause of the anaphylaxis and that this and suxamethonium should be avoided in future. This was documented in Sue’s medical notes, and she was provided with written information to carry with her.

Case study 3 – allergy to analgesia
Sayeed is a 54-year-old man who took ibuprofen and amoxicillin tablets after a tooth extraction. Approximately 45 minutes after taking these tablets, he developed widespread itch with facial and lip swelling.

He felt faint and called emergency services. He collapsed when the ambulance arrived and was treated with three doses of intramuscular adrenaline (epinephrine) and fluids.

Sayeed was referred to an allergy service for specialist investigation because it is necessary for him to take a non-steroidal anti-inflammatory drug (NSAID) for chronic back pain.

NSAIDs are reported to be the second most common cause of drug allergy after penicillin (Mirakian et al 2009, Ewan et al 2010). There are no validated blood or skin tests for NSAIDs; therefore, the only means of testing is an oral challenge, which is associated with a significant risk of precipitating an allergic reaction during testing. Therefore, in this case study, to exclude amoxicillin as a cause of the initial reaction, blood tests were undertaken, as were skin prick and intradermal tests for penicillin, which proved negative. Subsequently, an oral challenge with amoxicillin was undertaken, which also proved negative.

Managing drug allergy consists of both diagnosis and avoidance of the culprit drug. However, management may also require avoidance of chemically similar drugs and identification of suitable alternatives (Mirakian et al 2009, Ewan et al 2010, Odedra and Faroque 2014).

Given the severity of the initial reaction in this case study, it was felt that an ibuprofen challenge was too high risk. Therefore, a staged oral challenge with a Cox II drug was undertaken, in which a single adult dose of a drug was split and administered in three increasing amounts.

Cox II drugs work through a different pathway to Cox I drugs such as ibuprofen, and are generally tolerated by patients who have had allergic reactions to aspirin, ibuprofen and diclofenac (Sanchez-Borges et al 2001).

In this case study, Sayeed tolerated the Cox II drug, etoricoxib without any adverse effects and subsequently found it to be an effective analgesic.
The final stage of testing involves provocation testing, in which a full adult dose is given while the patient is monitored. This is usually done to exclude allergy to a drug. The drug may be given in several doses to reduce the risk of a severe reaction, and the doses are administered at specific time intervals depending on the absorption profile of the medicine and the timing of the original reaction. During this time, the patient is closely monitored for visible signs of an allergic reaction.

Testing requires written, informed consent from the patient and is undertaken in specialist centres by staff who have expertise in the diagnosis and management of drug allergy, and where there are facilities to promptly respond to and treat anaphylaxis, should it occur during testing. Occasionally, provocation testing may be used to confirm a diagnosis of drug allergy, but this is not recommended for patients who have experienced anaphylaxis, and is contraindicated for those who have experienced DRESS, SJS or toxic epidermal necrolysis.

Drug desensitisation

In some patients, it may be necessary to consider drug desensitisation. This is a procedure that induces temporary tolerance in a patient by gradual reintroduction of fixed drug doses at set time intervals (Mirakian et al 2009, 2015). However, to maintain this level of tolerance, the patient must continue to take the drug regularly, therefore, drug desensitisation is only undertaken in patients where the index drug is deemed to be essential. Typical cases include insulin allergy and antibiotic allergy in patients with a genetic infection such as cystic fibrosis (Parmer and Nasser 2005). Drug desensitisation has a risk of inducing anaphylaxis and must be undertaken in hospital by specialist staff.

Maintaining patient safety

It is essential to provide patients with a drug allergy notification letter containing details of the culprit drug, the signs and symptoms of the reaction, and suitable alternative medicines to assist in their long-term care (NICE 2014). In addition, patients should be advised to obtain and wear an engraved medical alert bracelet or necklace to inform healthcare professionals of their allergy or allergies in an emergency. It is also important to inform patients about the potential dangers of over-the-counter medicines and advise them to check with a pharmacist before purchasing these (Mirakian et al 2009, NICE 2014).

Patients with drug allergy do not usually require an adrenaline autoinjector; instead, they should be given clear advice and written guidance on how they can avoid the medicine they are allergic to. Inpatient strategies for indicating a patient has a drug allergy include the use of red wristbands and redesigning drug charts so that the allergies box is visible regardless of which page of the drug chart is open. Nurses must ensure that all ADRs are reported through the incident-reporting mechanism in their local healthcare organisation, and to the Medicines and Healthcare products Regulatory Agency via the online yellow card scheme (https://yellowcard.mhra.gov.uk) or via the British National Formulary (2017). Reporting ADRs can improve knowledge about their causes and prevalence and thus improve patient safety.

Case studies 1, 2 and 3 demonstrate the role of the nurse in managing, reporting and documenting drug allergies.

Conclusion

Drug allergies significantly affect patient morbidity and are associated with a risk of death. Awareness of this potential issue and early recognition and treatment of symptoms of drug allergy can improve patient outcomes. Specialist investigation is recommended for any patients experiencing drug anaphylaxis, reactions relating to general or local anaesthesia, severe systemic reactions or where avoidance of the drug – particularly antibiotics – is compromising patient care. Nurses may be involved in all aspects of drug delivery, including prescribing, administering and monitoring, and are well placed to document and report ADRs appropriately, discuss referral to an allergy service for specialist investigation with colleagues, and maintain patient safety.

References


