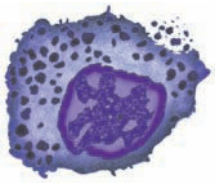

3. Drug hypersensitivity

Francis C K Thien

ABSTRACT

- Most drug reactions are pharmacological reactions rather than hypersensitivity reactions.
- In assessing drug reactions, a detailed clinical history and careful documentation of reactions are most important.
- Elucidating the nature and time course (first versus subsequent exposure, immediate versus non-immediate) of a reaction can help to distinguish immune from non-immune hypersensitivity, as well as IgE-mediated from T cell-mediated allergy.
- Skin testing and in-vitro tests are of predictive value for only a limited group of IgE-mediated drug allergic reactions.
- Drug provocation challenges can be used to eliminate suspicion of a low-probability drug reaction, find a safe alternative to a proven or probable drug reaction, or as a means of desensitisation.
- If a patient taking an angiotensin-converting enzyme (ACE) inhibitor develops angioedema, the cause must be assumed to be the ACE inhibitor until proven otherwise.

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Doctors are frequently faced with patients who report that they are "allergic" to a drug or a range of drugs. In some cases, further questioning reveals only scant information about a possible reaction in early childhood, with no recollection of the circumstances or reaction, and no documentation available; in other cases, detailed history taking reveals that the reaction was a side effect, intolerance or some other adverse drug reaction (ADR) rather than a true drug allergy. A common problem faced by doctors is trying to determine the specific cause of a possibly drug-related skin rash in patients taking multiple medications. Often there is also uncertainty as to whether the rash may be due to the underlying disease (eg, an infection) or to the antibiotic prescribed to treat it.

Trying to determine whether a causal relationship exists (and, if so, with which medication), the true nature of the reaction, and implications for future drug prescription can be a frustrating experience for both doctors and patients. Lack of knowledge and experience in this important area can lead to fear of multiple "drug allergies" and unnecessary avoidance of appropriate medications, with reliance on more expensive, or less effective, alternatives without a rational basis.

The pragmatic approach taken in my article is to consider carefully all patients presenting with a supposed "drug allergy", give a clinical framework to determine causality, and clarify which reactions are likely to be the result of true drug allergy in the context of all adverse drug reactions. Specialist procedures such as drug challenge or desensitisation are beyond the scope of my article, but the principles behind them will be explained. This will also help guide doctors as to which patients would benefit from referral for such investigation and management.

Adverse drug reactions

The World Health Organization defines an ADR as a response to a drug that is noxious, unintended or undesired occurring at doses normally used for the prevention, diagnosis or treatment of disease.[1] A pharmacological classification[2] divides most ADRs into one of two major subtypes: type A and type B reactions.

Type A reactions are pharmacological effects that are predictable and dose-dependent. Most ADRs (about 80%) are type A reactions, which include toxic effects (such as digoxin toxicity, and serotonin syndrome caused by selective serotonin reuptake inhibitors); side effects; secondary effects (eg, antibiotic-associated diarrhoea); and drug interactions.

Type B reactions are hypersensitivity reactions that are unpredictable and not dose-dependent. They lead to objectively reproducible symptoms or signs at a dose tolerated by normal people.[3] Type B reactions comprise about 10%–15% of all ADRs. Drug allergies, which comprise 5%–10% of ADRs,[4] are hypersensitivity reactions that involve an immune mechanism (IgE- or T cell-mediated, or, rarely, involving an immune complex or cytotoxic reaction). All other hypersensitivity drug reactions without an immune mechanism (5%–10%) — or in which an immunological process is not proven — are classified as non-immune (or non-allergic) hypersensitivity reactions (Box 1).[3]

Making the diagnosis

Clinical history: is it an adverse drug reaction?

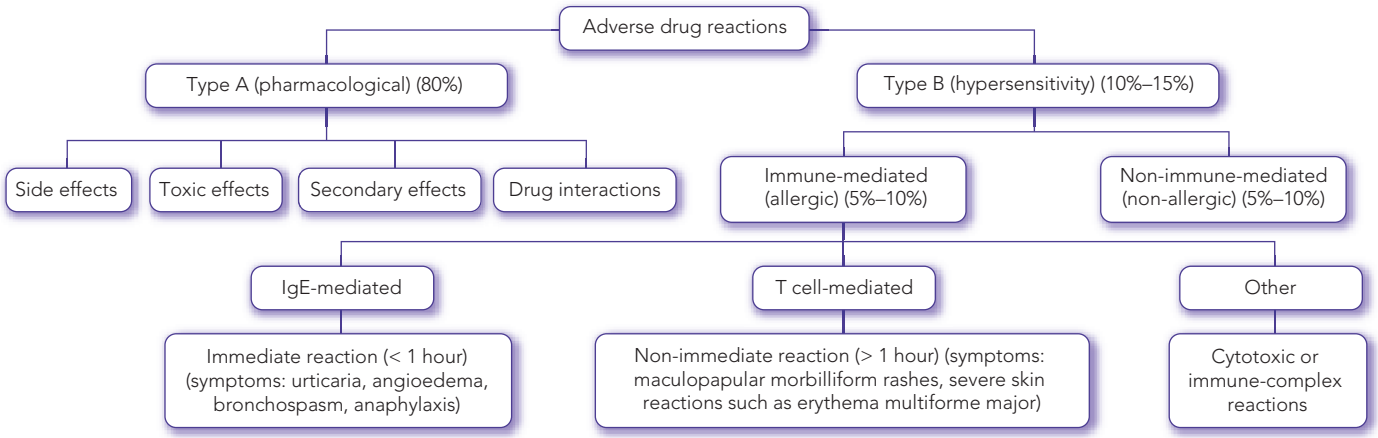
The most important step in assessing a possible ADR is to take a detailed clinical history — to assess causality, determine the underlying mechanism (pharmacological effect or hypersensitivity reaction) and assess whether the reaction may be allergic in nature (ie, immune-mediated hypersensitivity reaction). Careful documentation by the attending doctor of the circumstances and type of reaction of the suspected ADR is critical. Important initial questions on clinical assessment include the following:

- What was the temporal relationship between ingestion/administration of the drug and onset of the reaction?
- Was the nature of the reaction in keeping with known adverse reactions to the drug?
- Did the reaction resolve with cessation of the drug, and did it recur if the drug was recommenced?
- Were other drugs administered concurrently that could have caused the reaction?
- Was/Were there any underlying condition(s) of the patient that could explain the reaction?

If a clear clinical history and supportive documentation are available, a probability (or index of suspicion) can often be assigned to the likely cause. For example, a high probability can be assigned if there was a clear temporal relationship, a reaction consistent with known adverse reactions to the drug, an improvement after cessation of the drug or recurrence of a reaction after re-challenge, and no reasonable alternative explanation for the reaction (such as reaction to another drug or underlying condition).

The pharmacological features of type A adverse reactions (toxicity, side effects, secondary effects and drug interactions) can often

1 Classification of adverse drug reactions, including hypersensitivity and immune-mediated drug allergy



be determined by searches of pharmacological references and databases such as the *Australian medicines handbook*[5] or *MIMS annual*.[6] However, doctors are sometimes faced with an unclear history or lack of supportive documentation, making this important part of the evaluation indeterminate.

Clinical history: is it a true drug allergy?

If there is high probability of a causal relationship and the reaction is not pharmacologically mediated, the following three questions can help to distinguish immune-mediated (allergic) from non-immune-mediated hypersensitivity:

- Did the observed reaction occur on first exposure to the drug?
- What was the nature of the reaction?
- What was the time course of the reaction?

Did the observed reaction occur on first exposure?

Immunologically mediated reactions require previous exposure and time for an immune response (sensitisation) to develop. Hence, they do not usually occur the first time a drug is taken. It is not uncommon for a patient to be tolerant to the first course of a drug (during which they are sensitised) and then to experience a reaction on taking the first dose of the next course some weeks or months later. An exception to this is when there is previous sensitisation to another drug that has common antigenic determinants (eg, penicillin and cephalosporin have shared β-lactam determinants).

What was the nature of the reaction?

Urticaria, angioedema, bronchospasm and anaphylaxis signify mast cell activation, and usually indicate an immune mechanism mediated by drug-specific IgE antibodies (Box 2). However, some drugs (eg, radiocontrast media, aspirin or vancomycin) may activate mast cells directly, or through non-immune mechanisms, without previous exposure (Box 3).

Maculopapular exanthems such as morbilliform, fixed drug eruptions and other non-specific rashes are mediated by T cells. Hence, detailed history and documentation — such as getting the patient to take a photo of the rash, if it is transient — can often help to elucidate the nature of the reaction, distinguish between urticarial and morbilliform rashes, and guide appropriate testing and management.

Life-threatening conditions such as erythema multiforme major (Stevens–Johnson syndrome) and toxic epidermal necrolysis (Box 4), which cause widespread desquamation, mucosal ulceration and high fevers, are also mediated by T cells. The effector cells in these reactions are drug-specific memory T cells, but the exact mechanism is unclear.

What was the time course of the reaction?

Immediate reactions (occurring from several minutes to 1 hour after drug administration) suggest an IgE-mediated event caused by pre-formed IgE antibodies.

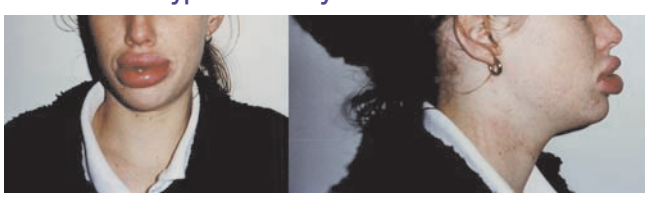
Non-immediate reactions (occurring more than 1 hour after drug administration) suggest a drug-specific T cell-mediated mechanism.[7] These late reactions may present in a variety of ways, including fixed drug eruptions, maculopapular morbilliform rashes, and bullous or pustular exanthems. Other non-cutaneous manifestations may include unexplained pyrexias, arthralgia, myalgia, eosinophilia or other haematological abnormalities, and derangement of liver function. These non-immediate reactions are not IgE-mediated, which has implications for diagnostic testing and management.

Detecting allergen-specific IgE

Skin testing

Skin testing (by skin prick or intradermally) is of predictive value for only a limited group of IgE-mediated drug allergic reactions. The best characterised drug is penicillin, for which the immunogenic isotopes (the parts of the molecule recognised by the immune system) have been identified. They consist of a major

2 Florid lip and face angioedema due to β-lactam immediate hypersensitivity



determinant (accounting for 95% of penicillin degradation metabolites) and minor determinants (accounting for 5% of metabolites). Testing with major and minor determinants is done with a skin prick test, followed by an intradermal test if the skin prick test is negative. (The commercial product Pre-Pen [Hollister-Stier], which contains the major determinant of penicillin, is currently unavailable anywhere, but alternatives may be available in the near future.) A weal diameter of at least 3 mm greater than that of the negative control, together with erythema, constitutes a positive test. US studies have shown that a negative test in patients with an indeterminate clinical history indicates that penicillin can be administered with less than 4% risk of an immediate reaction[8] (similar to the risk in the general population). However, more recent European research indicates that the predictive value is much lower in patients with a documented high probability clinical history of immediate reaction.[9]

Amoxycillin and ampicillin should be included in the skin test array to improve the diagnostic value.[10] This is because, with changes in drug prescription patterns, some patients are developing immunological reactivity to β-lactam sidechains specific to amoxycillin and ampicillin molecules, rather than the classical major and minor determinants common to all synthetic penicillin β-lactams.

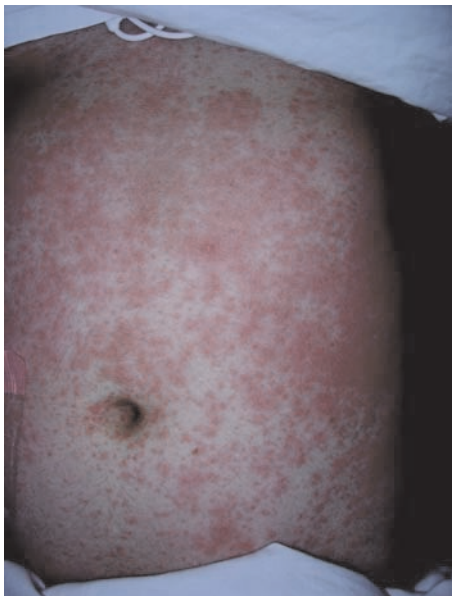
Other drugs for which skin prick and intradermal tests are of predictive value include muscle relaxants, insulin, and biological agents such as Gelofusine (B. Braun) (a plasma volume expander) and streptokinase. Patch tests are done by making a 5% concentration of the relevant drug in a vehicle such as petrolatum, applying it to the skin and measuring the reaction after 48–72 hours. They are used to study non-immediate reactions, although their clinical diagnostic value is limited.[11] However, for the vast majority of allergic drug reactions, there are no validated skin tests that have been shown to be of predictive value. This is because the reactions are either not IgE-mediated, or the relevant immunogenic epitopes (which may be derived from unidentified drug metabolites or breakdown products) have not been identified for most drugs.

Blood specific IgE testing

The radioallergosorbent test (RAST) and the non-radioactive enzyme-linked immunosorbent assay (ELISA) are commercially available in-vitro tests for detecting serum specific IgE antibodies. The tests are only available for some β-lactam antibiotics, as the immunogenic epitopes for most drugs are unknown. Like other in-vitro tests, they are generally more specific but less sensitive than skin tests. Hence, they have poor negative predictive values but better positive predictive values, and are used in conjunction with clinical evaluation and skin tests.[10]

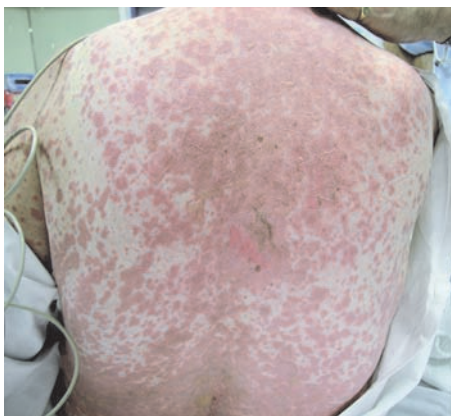
The lymphocyte transformation test detects drug-specific T cells, which may be involved in some delayed allergic hypersensitivity reactions, but this is used for research purposes and has limited clinical application.[12]

3 Immediate hypersensitivity urticarial rash secondary to vancomycin administration



Courtesy of Department of Dermatology, Alfred Hospital, Melbourne. ◆

4 Toxic epidermal necrolysis secondary to sulfasalazine administration



Courtesy of Department of Dermatology, Alfred Hospital, Melbourne. ◆

Evaluation: to challenge or not?

A drug provocation challenge is the controlled, graded administration of a drug in order to diagnose a drug hypersensitivity reaction. There are three situations in which a drug provocation challenge may be considered when evaluating allergic drug hypersensitivity:

- When the clinical evaluation suggests low or indeterminate clinical probability of a causal relationship between the drug and the ADR, the reaction is not severe, and skin or in-vitro tests are not available or helpful, a drug provocation challenge may be considered, to eliminate suspicion and allow the drug to be used in future;
- When clinical evaluation suggests a moderate to high probability that a particular drug was the cause of an ADR and a safe alternative is required, another chemically or structurally different or unrelated drug may be given under monitored challenge to exclude the possibility of cross-reactivity between the two drugs;
- When a drug is implicated with high probability (with or without supportive skin and in-vitro tests, if available) and is the drug of choice, a drug provocation challenge may be given to confirm the diagnosis, followed (if positive) by desensitisation (see below) and therapeutic administration of maintenance doses.

The general principle of a drug challenge is to start at a very low dose (well below the normal therapeutic dose) and give repeated administration at increasing (usually doubling) doses of the drug until a threshold of reaction is reached, when first objective symptoms occur. (If no symptoms appear, the challenge stops when the therapeutic dose is reached.) Intervals between dosing may range from 15 minutes to several hours, depending on the drug, and it may be given orally or intravenously.

Provocation tests should be done in specialised clinics or hospitals with established protocols and resuscitation facilities, and should never be conducted in patients with a history of severe, life-threatening vasculitic syndromes, exfoliative dermatitis, erythema multiforme major, drug-induced hypersensitivity reactions with eosinophilia, or toxic epidermal necrolysis.[13]

Management of ADRs

The approach to the patient with a suspected ADR must be very methodical (Box 5). Firstly, as outlined above, a causal relationship must be established between the drug and the reaction. Then the reaction type must be determined, if possible.

For type A (pharmacological) drug reactions, dosage modification may be all that is necessary before drug re-administration. Toxicity, as well as drug-induced side effects and secondary effects (eg, nausea and vomiting caused by opiates, or antibiotic-associated diarrhoea) may resolve at lower drug doses.

For type B (hypersensitivity) drug reactions, several options may be considered. After severe or life-threatening reactions, the drug should not be re-administered. For less severe reactions, a drug provocation challenge may be considered. For type B immunologically-mediated (allergic) reactions, the management option depends on the mechanism responsible for the reaction. If validated confirmatory tests are available, they should be used to determine the allergic status of the patient (eg, tests for penicillin-specific IgE antibodies). If such tests are not available — and in most cases they are not — several approaches can be taken. The simplest approach is to avoid the drug if an alternative agent is available. If an alternative drug does not exist, a graded challenge with the implicated agent can be done if the previous reaction was not life-threatening and not consistent with an IgE-mediated reaction. However, if the medication is needed as the drug of choice, then desensitisation should be considered.[14]

Desensitisation

Desensitisation is possible for many drugs by continuing repeated administration of doubling doses after a positive drug challenge until a therapeutic dose is reached. (The desensitisation process is identical to a drug challenge, except that a drug challenge is stopped when a positive reaction occurs, whereas, in desensitisation, drug administration is continued in spite of an initial mild reaction.) The mechanism of drug desensitisation is not well understood, but may, in some cases, involve controlled degranulation of mast cells. However, the desensitised state is not permanent — in contrast to some allergen immunotherapy (eg, bee venom immunotherapy) — and is sustained only with a daily maintenance dose of the drug. Cessation of the maintenance dose will allow the drug hypersensitivity to return, usually within a few days, and subsequent administration will require a repeated desensitisation process if the maintenance drug has been stopped. Drugs for which desensitisation may be successful include allopurinol, cotrimoxazole, β-lactam antibiotics and aspirin.

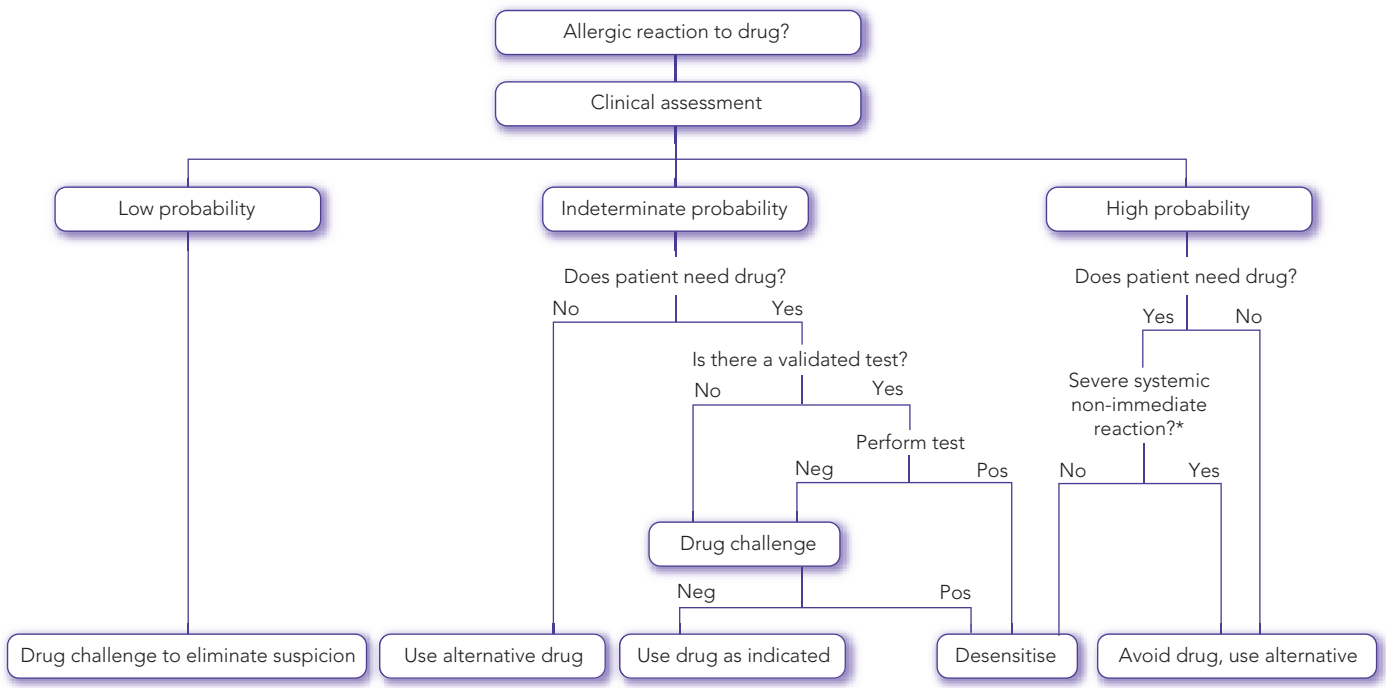
Some specific drugs

β-lactam antibiotics

Allergic reactions to β-lactam drugs are the most common group of type B hypersensitivity ADRs. The clinical, diagnostic and management approach to IgE-mediated immediate penicillin allergy has already been discussed (see "Detecting allergen-specific IgE: skin testing", above).[15] For the majority of reactions that produce non-immediate exanthems (and are probably mediated by T cells rather than IgE), the approach depends on the severity of the reaction and the potential need for penicillin-based therapy in the future.

Lifelong avoidance of a drug is necessary for the rare but severe reactions such as erythema multiforme major or toxic epidermal necrolysis. With more common morbilliform maculopapular exanthems, as seen when amoxycillin is administered concurrently with a viral infection (eg, infectious mononucleosis), the exact mechanism is not clear, but may be due to viral infection altering

5 Management of drug allergy



* Severe systemic non-immediate reactions include erythema multiforme major (Stevens–Johnson syndrome) and toxic epidermal necrolysis. ◆

6 Case scenario*

A 45-year-old man who was previously well (apart from mild seasonal hayfever, treated occasionally with antihistamine) presented for review of a recent documented anaphylactic reaction. He had woken one morning with a sore knee, for which he took a tablet of naproxen 500 mg after his usual breakfast. Within 10 minutes (while sitting on the toilet), he felt itching on his scalp, which became generalised. When he got up to wash his hands, he felt dizzy and fainted. On regaining consciousness (within a minute, according to his wife), he felt shortness of breath and the need to open his bowels again. When he fainted again, this time on the toilet seat, his wife rang for an ambulance.

At the hospital emergency department, he was noted to be faecally incontinent, with an unrecordable blood pressure and slow respiration. Treated with adrenaline, intravenous fluids and steroids, he recovered within an hour and was discharged the following day.

On further questioning, it was found he had injured his knee while playing football and had taken a 1-week course of naproxen within the previous 3 months, with no side effects. He had taken no other medications at that time.

In this case, naproxen was the "smoking gun", with no other reasonable or rational alternative explanation for the witnessed events. No supportive skin or in-vitro tests are available for naproxen or other non-steroidal anti-inflammatory drugs (NSAIDs). As there were no alternative explanations, a confirmatory drug challenge was not needed; in any case, the severity of the reaction ethically precluded it. However, the issue of whether the patient could take other NSAIDs or aspirin for future cardiovascular prophylaxis was an important one to resolve.

The patient had no history of asthma or nasal polyposis (for which the clinical syndrome includes sensitivity to all cyclo-oxygenase-1 [COX-1] inhibitors), suggesting that this was a single-drug immune hypersensitivity reaction. The reaction was possibly mediated by an as yet unidentified IgE mechanism — perhaps involving sensitisation after the previous course of naproxen.

A negative reaction on challenge with aspirin confirmed that the mechanism of the patient's anaphylactic reaction was not COX-1 inhibition, and that he could take aspirin safely for cardiovascular prophylaxis in future. He was also challenged with diclofenac, which is structurally unrelated to naproxen, to which he had no reaction. Thus, he was advised to use diclofenac in the future if an NSAID was required. He was instructed to avoid naproxen lifelong, as well as its structurally related NSAIDs (including ibuprofen, ketoprofen and flurbiprofen), in order to avoid possible, but as yet unproven, immune cross-reactivity to structurally related drugs.

* This is a fictional case scenario based on similar real-life cases. ◆

the immune status of the host. In this situation, the drug can be administered safely again once the viral infection has resolved,[16] highlighting the critical role of taking a detailed clinical history and making a careful assessment.

When a patient with immediate penicillin allergy requires an alternative β-lactam drug, consideration can be given to prescribing a cephalosporin. A review of 11 studies of cephalosporin administration to patients with a history of penicillin allergy found cephalosporin reactions in 4.4% of patients with positive skin tests for penicillin.[17] A practical approach is to ascertain whether the previous penicillin reaction was an immediate IgE-mediated allergy, and, if not, a graded challenge can be performed to determine whether the cephalosporin is a safe alternative. If the previous penicillin reaction was immediate, evaluation with penicillin skin testing should be done first.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Hypersensitivity reactions to aspirin and other NSAIDs may have a number of clinical manifestations. One clinical syndrome is late-onset asthma (onset age in the 30s or 40s) with nasal polyposis, and later development of aspirin hypersensitivity, with NSAID ingestion provoking asthma and rhinitis. This may affect 5%–10% of people with asthma. It involves a non-immune hypersensitivity mechanism of increased leukotriene production caused by inhibition of the cyclo-oxygenase-1 (COX-1) enzyme.[18] Such people are sensitive to aspirin and all older non-specific NSAIDs, but tolerate specific COX-2 inhibitors (such as celecoxib). However, there are other clinical syndromes in which there is no history of asthma or rhinitis and the patient has an isolated sensitivity to a specific NSAID.[19] This may have an immunological basis with a putative IgE mechanism. Clarifying the history and recognising the clinical patterns can allow specific provocation challenges to ascertain safe alternatives and prevent unnecessary avoidance of aspirin or other NSAIDs (see Box 6).

Angiotensin-converting enzyme (ACE) inhibitors

Angioedema is a well recognised adverse reaction that affects 0.1%–0.5% of patients taking ACE inhibitors.[20] Angioedema can first appear anywhere from a few hours to 8 years after an ACE inhibitor is taken, with up to 20% of cases being life-threatening.[20] The reaction involves a non-immune hypersensitivity mechanism caused by the accumulation of plasma kinins (such as bradykinin) as the result of inhibition (by ACE inhibitors) of the kininases that normally metabolise and inactivate bradykinin.[21] If a patient taking an ACE inhibitor develops angioedema, the cause must be assumed to be the ACE inhibitor, and the drug should be ceased immediately (until such time as the drug is proven not to be the cause) (Box 7). Rare instances of angioedema have also been reported after taking angiotensin-receptor antagonists, but these reactions may not be mediated by bradykinin.

Sulfonamide antibiotics

Delayed reactions, such as maculopapular exanthems, associated with cotrimoxazole are probably mediated by T-cell responses to reactive sulfonamide metabolites. There is increased frequency of these reactions in certain clinical situations (eg, they affect 20%–80% of patients infected with HIV, compared with 1%–3% of non-HIV-infected patients, possibly due to altered drug metabolism).[10] Management is by avoidance, but desensitisation is possible in some cases.

Another common clinical problem is the putative cross-reactivity between sulfonamide antibiotics and other sulfonamide-derived drugs (eg, diuretics, sulfonylureas, celecoxib and sumatriptan). Patients may report that they are "allergic" to "sulfur antibiotics". Although the true nature of their reaction may often be obscure, they are excluded from taking drugs in these groups

7 Evidence-based practice tips*

- Drug desensitisation can allow safe administration of the drug in immediate hypersensitivity reactions, even in cases of anaphylaxis (Level III-3).
- If a patient taking an angiotensin-converting enzyme (ACE) inhibitor develops angioedema, the cause must be assumed to be the ACE inhibitor until proven otherwise (Level IV).

* Based on National Health and Medical Research Council levels of evidence.[22] ◆

Fact or fiction – true or false?

1. The majority of drug allergies can be investigated by validated and predictive skin tests (T/F)
2. Desensitisation is possible for many drug allergies, but a daily dose is required to maintain the desensitised state (T/F)
3. Patients with a history of sulfonamide antibiotic allergy cross-react to other drugs with a sulfonamide component (such as diuretics, sulfonylureas or celecoxib) and should avoid these drugs and dietary sulfites (T/F)

1. False. Validated and predictive skin tests are only available for a limited group of IgE-mediated allergic reactions to drugs, the best characterised of which is penicillin.
2. True. Desensitisation is achieved by repeated administration of increasing doses of the relevant drug, starting at a very low dose, until the threshold of reaction is reached. However, the desensitised state is sustained only with a daily maintenance dose of the drug.
3. False. Potential cross-reactivity of sulfonamide antibiotic allergy with non-antibiotic sulfonamide drugs has not been borne out in clinical practice, and need not necessarily exclude their use if clinically indicated. ◆

because of concern about supposed cross-reactivity with their sulfonamide component. However, this is only a theoretical concern that has not been borne out in clinical practice, and need not necessarily exclude their use if clinically indicated.[23] Furthermore, there is no relationship between sulfonamide allergy and intolerance to sulfite preservatives in food.

When to refer

In assessing ADRs, it is important for physicians to distinguish between those that represent hypersensitivity from those that are pharmacological. If possible, hypersensitivity reactions need to be differentiated further into those that are truly allergic in nature and those that are not immunologically mediated. Clinical evaluation is the most important means of assessment, with supportive skin tests and laboratory tests helpful if validated and available. Referral for specialist assessment is warranted:

- for early assessment of possible drug reactions when the mechanism of reaction is unclear;
- for advice on distinguishing sulfur antibiotic reactions from risk of reaction to sulfur-containing non-antibiotics or dietary sulfites;
- for assessment of severe reactions, such as toxic epidermal necrolysis;
- when avoidance of a particular drug is not an option;
- to help choose a suitable NSAID when a patient has reacted to a drug in this class; or
- when considering desensitisation if an implicated medication is the drug of choice.

However, until we have a better understanding of the mechanisms responsible for hypersensitivity drug reactions, our management tools will remain limited.

Acknowledgements

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Competing interests

I am on advisory boards for GlaxoSmithKline and Reckitt Benckiser, for which I receive honoraria. I have received speaker fees from GlaxoSmithKline, Schering-Plough, AstraZeneca and Boehringer-Ingelheim, and travel assistance to attend international meetings from GlaxoSmithKline and AstraZeneca.

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