ABC of allergies
Adverse reactions to drugs

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Definition

An adverse reaction to a drug has been defined as any noxious or unintended reaction to a drug that is administered in standard doses by the proper route for the purpose of prophylaxis, diagnosis, or treatment. Some drug reactions may occur in everyone, whereas others occur only in susceptible patients. A drug allergy is an immunologically mediated reaction that exhibits specificity and recurrence on re-exposure to the offending drug.

Incidence

Adverse reactions to drugs are very common in everyday medical practice. A French study of 2067 adults aged 20-67 years attending a health centre for a check up reported that 14.7% gave reliable histories of systemic adverse reactions to one or more drugs. In a Swiss study of 5568 hospital inpatients, 17% had adverse reactions to drugs. Fatal drug reactions occur in 0.1% medical inpatients and 0.01% of surgical inpatients. The main drugs implicated are antibiotics and non-steroidal anti-inflammatory drugs. Adverse reactions to drugs occurring during anaesthesia (muscle relaxants, general anaesthetics, and opiates), although less common (1 in 6000 patients receiving anaesthesia), are life threatening, with a mortality of about 6%.

Numerous mechanisms have been implicated in adverse reactions to drugs. However, these mechanisms are not fully understood, which may explain the difficulty in differentiating drug allergy from other forms of drug reactions and in assessing the incidence of drug allergy, evaluating risk factors, and defining management strategies.

Mechanisms

Allergic reactions to drugs are classified according to Coombs' types I-IV. Most drugs (penicillins, sulphonamides) have low molecular weight (haptens) and are bound to proteins before being recognised by lymphocytes or antibodies. Pseudoallergic reactions to drugs may mimic these immunological mechanisms—for example, by direct release of histamine by opioids or complement activation by radioactive contrast media.

Risk factors

Adverse drug reactions occur mainly in young and middle aged adults and are twice as common in women. Genetic factors may be important. A familial predisposition to antimicrobial drugs has recently been reported. The HLA type may predispose to reactions to aspirin (HLA-DQw2) and insulin allergy (B7DR2, DR3). The slow *N*-acetylation phenotype may predispose to sulphonamide reactions—particularly common in patients with HIV infection. The role of atopy in predisposing to drug reactions is controversial. It may be important in reactions to iodinated contrast material but not to penicillin or reactions during anaesthesia. Risk factors relating to drugs themselves include macromolecular size (large molecules may be complete antigens—for example, insulin); bivalence (ability to cross link receptors—for example, succinyl choline); and the ability to act

Classification of adverse reactions to drugs

Reactions that may occur in anyone

Drug overdose—Toxic reactions linked to excess dose or impaired excretion, or to both

Drug side effect—Undesirable pharmacological effect at recommended doses

Drug interaction—Action of a drug on the effectiveness or toxicity of another drug

Reactions that occur only in susceptible subjects

Drug intolerance—A low threshold to the normal pharmacological action of a drug

Drug idiosyncrasy—A genetically determined, qualitatively abnormal reaction to a drug related to a metabolic or enzyme deficiency

Drug allergy—An immunologically mediated reaction, characterised by specificity, transferability by antibodies or lymphocytes, and recurrence on re-exposure

Pseudoallergic reaction—A reaction with the same clinical manifestations as an allergic reaction (eg, as a result of histamine release) but lacking immunological specificity

Mechanisms of drug allergy

Type I*	Immediate hypersensitivity, IgE mediated	Anaphylaxis, urticaria, angio-oedema, bronchospasm
Type II	Cytotoxic reactions, IgG and IgM mediated	Cytopenia, vasculitis
Type III	Immune complex reactions, IgG and IgM mediated	Serum sickness, vasculitis
Type IV	Lymphocyte mediated reactions	Contact sensitivity

*Non-specific complement activation and non-specific histamine release may mimic type I reactions

Risk factors for drug allergy

Patient related

Age, sex, genetics, atopy, AIDS

Drug related

Macromolecular size; bivalency, haptens; route, dose, duration of treatment

Aggravating factors

β Blockers, asthma, pregnancy

as haptens. Sensitisation may be dependent on route of administration; it occurs most commonly with the local route, less commonly with the parenteral route, and least often with the oral route. Intravenous administration gives rise to more severe reactions. β Blocking drugs inhibit the patient's response to adrenaline given to treat anaphylaxis.

Asthma and pregnancy may exacerbate adverse reactions to drugs

Diagnosis

Clinical history

Evaluation of drug allergy must begin with a precise and detailed history, including clinical symptoms and their timing and duration in relation to drug exposure. Reactions may be immediate (as in anaphylaxis, bronchospasm, urticaria, or angio-oedema); accelerated (occurring within 3 days (as in urticaria, asthma)); or late (occurring >3 days after first receiving the drug). Late reactions include mucocutaneous syndromes (rashes, exfoliative dermatitis) or haematological type (anaemia, thrombocytopenia, neutropenia).

As with other allergic diseases, true drug allergy requires prior exposure (sensitisation), and symptoms occur typically after the first dose of a subsequent course

Clinical manifestations of drug allergy

Manifestation	Clinical features	Examples of drugs
Anaphylaxis	Urticaria or angio-oedema, rhinitis, asthma, abdominal pain, cardiovascular collapse	Penicillin, neuromuscular blocking drugs
Pulmonary	Interstitial pneumonitis	Amiodarone, nitrofurantoin chemotherapeutic agents
	Asthma	Aspirin, non-steroidal anti-inflammatory drugs, β blockers
Hepatic	Acute or chronic hepatitis	Halothane, chlorpromazine, carbamazepine
Haematological	Haemolytic anaemia	Penicillin, α-methyldopa, mephenamic acid
	Thrombocytopenia	Frusemide, thiazides, gold salts
	Neutropenia	Penicillin
	Agranulocytosis	Phenylbutazone, chloramphenicol
	Aplastic anaemia	Non-steroidal anti-inflammatory drugs, sulphonamides
Renal	Interstitial nephritis, nephrotic syndrome	Cimetidine
Cardiac	Eosinophilic myocarditis	α-methyldopa
Other	Serum sickness, drug fever, vasculitis, lymphadenopathy	Anticonvulsants, diuretics, antibiotics, hydralazine, procainamide, penicillamine

Diagnostic tests

Skin prick tests may be helpful for diagnosing IgE dependent drug reactions, although occasionally positive results to skin prick testing may result from non-specific histamine release independent of IgE (for example, propofol, atracurium). Radioimmunoassays (for example, the radioallergosorbent test (RAST)) may detect serum IgE antibodies to certain drugs (penicillin and succinyl choline) and latex, which may be responsible for reactions during general anaesthesia that are unrelated to drugs. The same reservations apply as for skin tests.

Tryptase is a valuable marker of mast cell degranulation and may be helpful in the differential diagnosis of anaphylaxis. Serum tryptase concentrations peak one hour after anaphylactic reactions but may be detected several hours later. Serum samples at between 30 minutes and 5 hours after the event, when compared with baseline concentrations taken weeks after, may confirm or exclude the diagnosis.

Immediate skin testing for diagnosing IgE dependent allergy

Antibiotics
- Penicillin
- Cephalosporins

Anaesthetic drugs
- Muscle relaxants
- Thiopentone

Enzymes
- Chymopapain
- Streptokinase

Chemotherapeutic drugs
- Cisplatin

Others
- Insulin, latex

False positive and false negative reactions may occur with these skin tests

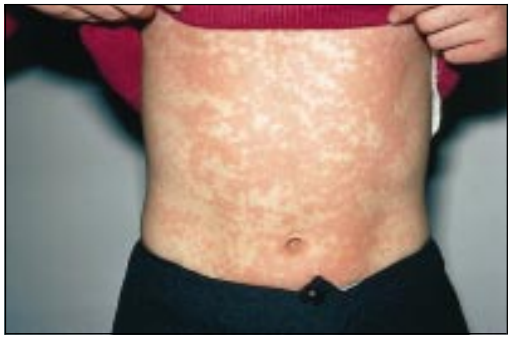
Provocation tests
Oral provocation tests, although seldom required, may be regarded as the "gold standard." They must be performed under strict medical supervision with resuscitative equipment available.

Drug reactions and the skin

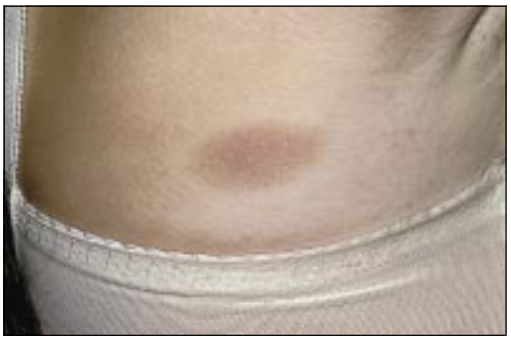
Drug induced rashes are the commonest side effect of many drugs. In general, the mechanisms are unknown, and only about 10% of such reactions result from true allergic mechanisms. Typical examples of drug induced rashes include erythematous maculopapular eruptions, fixed drug eruptions, erythema multiforme, and exfoliative dermatitis.

Cutaneous reactions to drugs

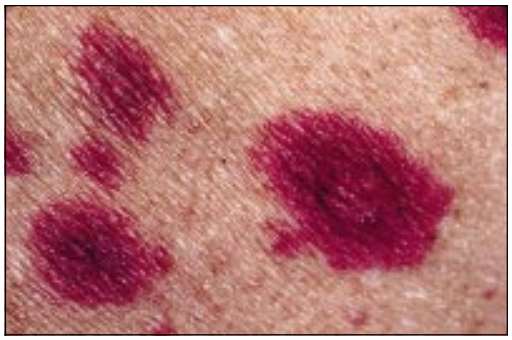
Manifestation	Examples
Pruritis, urticaria or angio-oedema, maculopapular rash	Most drugs
Contact dermatitis	Antibiotics, ethylenediamine
Photodermatitis	Griseofulvin, sulphonamides
Fixed drug eruption	Metronidazole, penicillin
Toxic epidermal necrosis (potentially life threatening)	Sulphonamides, phenytoin, carbamazepine, barbiturates, allopurinol, etc



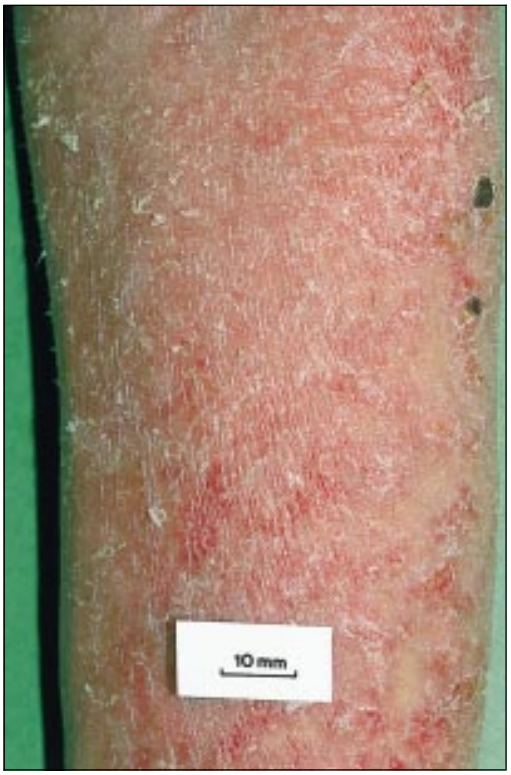
Erythematous maculopapular eruption due to penicillin: rashes of this kind are by far the most common reactions to drugs



Fixed drug eruption, so called because the lesion recurs at the same site after each administration—in this case, due to barbiturates



Erythema multiforme due to sulphonamide treatment, showing characteristic target-like lesions



Exfoliative dermatitis—a severe complication in this case due to co-trimoxazole

Management

Avoidance
As a general rule, a drug responsible for an allergic reaction should not be reused, unless there is an absolute need and no alternative drug is available. This is seldom the case with antibiotics, the commonest cause of allergic reactions.

Premedication
Pretreatment with H_1 antihistamines should not be used as they do not prevent anaphylactic shock and may mask early signs. However, in association with H_1 antihistamines, corticosteroids have been shown to be effective in reducing reactions to radioactive contrast media.

Desensitisation
Desensitisation should be considered in patients who have experienced IgE mediated allergic reactions to penicillin and who require penicillin for the treatment of serious infections—for example, bacterial endocarditis and meningitis. Protocols using oral and parenteral routes have been proposed. Oral administration is preferred because it is less likely to provoke a life threatening reaction. Desensitisation may occasionally be indicated for other antibiotics—for example, sulphonamides, cephalosporins—under specialist supervision.

In the rare cases when penicillin desensitisation is indicated, the penicillin is best administered orally in specialist centres—side effects are then infrequent and usually mild (pruritis or rashes)

Diagnosis of specific drug reactions

Muscle relaxants
Muscle relaxants are responsible for an anaphylactic reaction in 1 in 4500 general anaesthesias. The mechanism is IgE dependent. Diagnosis depends on the history supported by a positive result to skin prick testing or presence of serum allergen specific IgE by the radioallergosorbent test, or both of these.

Narcotics
Although opioid analgesics are the most commonly prescribed drugs, anaphylactic reactions are rare. Some narcotics (for example, morphine) are able to induce histamine release. Others, such as fentanyl, do not.

Local anaesthetics
Reactions are seldom related to the local anaesthetic itself. Most general reactions are not allergic but are the result of vasovagal attacks. IgE mediated reactions are the exception. Reactions may be due to adjuvants or preservatives or the injection technique. Associated drugs that may be responsible include adrenaline (epinephrine), sulphites, parabens, antibiotics. Skin prick tests using local anaesthetics have a high rate of false negative and false positive reactions but are useful as part of an incremental drug challenge ending with the standard therapeutic dose administered subcutaneously.

Antibiotics
Immediate-type reactions to penicillin may be diagnosed by skin prick tests, which should include both the major determinant (penicilloyl polylysine) and the minor determinant mixture (benzylpenicillin, penilloate, MDM). Skin tests are not helpful for other manifestations of penicillin allergy (contact dermatitis, exfoliative dermatitis, etc). Skin prick tests with other antibiotics (for example, cephalosporins, amoxycillin, clavulinic acid, and aztreonam) may be performed. Skin prick tests with antibiotics other than penicillin have a high false negative rate, although a positive result may provide supportive evidence for a clinical history suggestive of an IgE mediated reaction.

The slides for the four photographs of drug induced skin reactions were provided by Dr Rino Cerio, consultant dermatologist at the Royal London Hospital, and Dr William F Jackson, and published with permission from *A Colour Atlas of Allergic Skin Disorders* (Wolfe, 1992).

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The ABC of allergies is edited by Stephen Durham, honorary consultant physician in respiratory medicine at the Royal Brompton Hospital, London. It will be published as a book later in the year.

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Radiocontrast media

- The incidence of reactions to radiocontrast media is between 4.6% and 8.5% of procedures
- Anaphylaxis occurs in 1% and death in 0.001-0.009% of patients who receive radiocontrast media
- The mechanism is unknown but may relate to complement activation
- Newer contrast media with low osmolarity are much safer, although life threatening reactions may still occur
- There are no diagnostic tests
- Atopy is a predisposing factor, and patients with a previous reaction have a 17-35% chance of recurrence on re-exposure
- Prevention of reactions involves the use of newer radiocontrast media and premedication with oral corticosteroids and antihistamines in patients at risk

Aspirin and non-steroidal anti-inflammatory drugs

- Aspirin may induce anaphylaxis, urticaria, asthma, rhinitis, angio-oedema, Lyell's syndrome, purpura, and photodermatitis
- About 20% of asthmatic adults are sensitive to aspirin
- Associated reactions to other non-steroidal anti-inflammatory drugs are common, such that all should be avoided in patients sensitive to aspirin
- The mechanism may be related to inhibition of prostaglandin synthesis with overproduction of leukotrienes
- In cases of diagnostic doubt oral challenges may be performed (these are dangerous in patients with asthma, in whom bronchial inhalation provocation with lysine aspirin is the safer option)
- Paracetamol is tolerated by most but not all patients who are sensitive to non-steroidal anti-inflammatory drugs

Further reading

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