REVIEW ARTICLE

Drug allergy

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Abstract **Drug allergy is an important complication in the use of agents such as penicillins, cephalosporins, sulphonamides, insulin and streptokinase. The allergenic properties of drugs are a function of molecular size and chemical reactivity. Factors determining an individual's risk of an allergic response are not fully understood but include genetic predisposition, prior exposure, route of administration, drug dosage, age and concomitant disease.**

The most dangerous but least common form of drug allergy is generalised anaphylaxis. The majority of reactions are non-anaphylactic and involve the skin, with a lesser incidence of haematological, renal, musculoskeletal, cardiorespiratory and other systemic manifestations.

The only definitive test for allergy in a patient with a history of previous allergic reaction is rechallenge, a dangerous and seldom indicated procedure. An alternative is skin testing, but this requires an experienced practitioner and has intrinsic risk. *In vitro* testing may be of value in predicting the risk of rechallenge.

Safe use of a suspect drug requires a careful assessment of risk and a cautious approach. Use of an offending drug in a high-risk patient is rarely indicated, but if it is considered essential, initial therapy or desensitisation in an intensive care environment is recommended.

S Afr Med J 1994; **84**:.281-286.

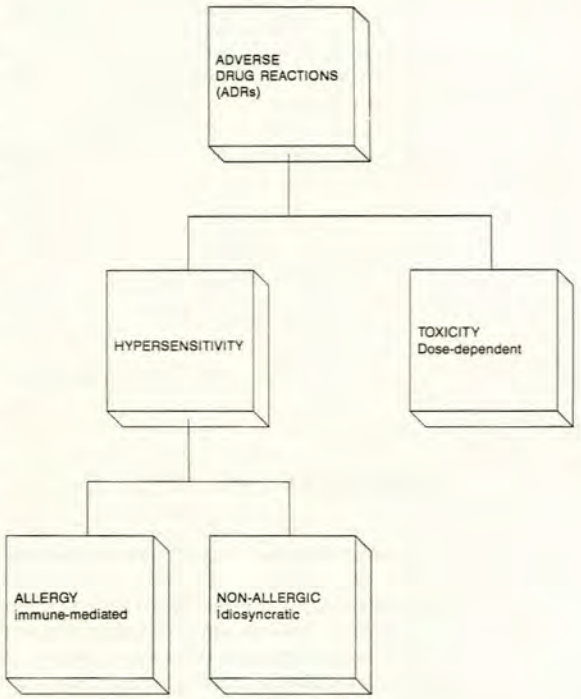

FIG. 1.
Definition of ADRs.

Drugs are an important cause of morbidity and mortality in modern medicine, with adverse drug reactions (ADRs) responsible for at least 1% of hospital admissions.[1]

Most ADRs are due to dose-related toxicity. A small proportion are hypersensitivity reactions which are not directly dose-related and due to aberrant drug kinetics or individual patient sensitivity. Drug allergy (immune-mediated hypersensitivity) accounts for 5 - 10% of ADRs[2-5] (Fig. 1).

Few drugs are likely to be antigenic. Most drugs are too small (molecular weight (MW) < 1 000) to be complete antigens and have a stable chemical nature preventing the conjugation with carrier molecules necessary for function as a hapten.[6] Metabolites of β-lactam antibiotics are an exception, with spontaneous disruption of the β-lactam ring yielding reactive groups which readily haptenate proteins to form complete antigens.[5] Most clinically important drug allergy and over 80% of life-threatening allergic reactions are caused by penicillin.[3,7]

Although sporadic drug allergy has been described for almost all drugs used, it is only a consistent risk for the β-lactams, sulphonamides and larger molecules such as insulin and streptokinase. The mechanism of sulphonamide allergy is poorly understood.[8] Several groups of drugs may cause clinical anaphylaxis in susceptible patients by a mechanism which does not involve immune recognition and antibody production; this phenomenon is thus not truly allergic in nature. Opiates,[5] non-steroidal anti-inflammatory drugs (NSAIDs)[4] and radiographic contrast media cause direct mast cell degranulation and mediator release.

IgG aggregates in administered immunoglobulin can activate complement components.[5] Activated complement factors C3a and C5a may then activate mast cells, causing an anaphylactic reaction.[8,9,10]

This review will discuss the mechanisms and epidemiology of drug allergy, with special reference to penicillin, and will suggest strategies for safer use of β-lactam antibiotics.

The mechanism of drug allergy

The tripeptide analogue penicillin (MW 356) degrades spontaneously in solution with opening of the β-lactam ring to form the penicilloyl group. Ten per cent of a dose will be degraded to metabolites that combine covalently with the lysine residues of serum tissue, membrane and microbial-derived proteins to form complete antigens.[3,5,11] The penicilloyl-protein carrier molecules are designated the 'major determinants' because they comprise 95% of the penicillin metabolites. The remaining 5% comprise several metabolites known collectively as the 'minor determinants' (Fig. 2). These terms refer only to the proportion of metabolites formed and not to their potency. Minor determinants are believed to be mainly responsible for severe acute allergic reactions,[2,3,12,13] while major determinant metabolites are more likely to elicit the lesser non-immediate penicillin reaction of urticaria.[12]

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Accepted 24 Mar 1993.

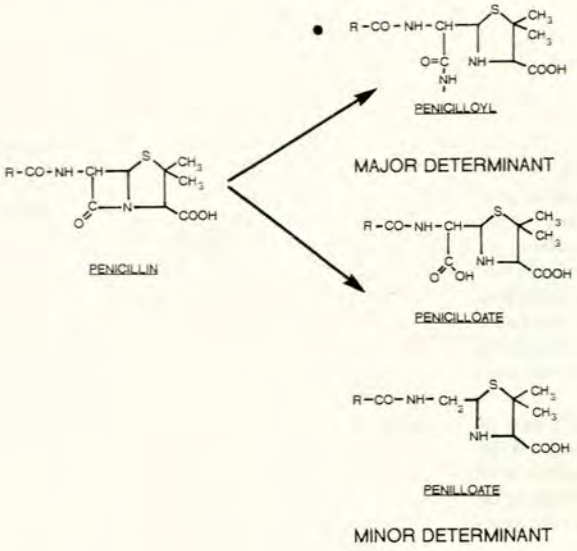


FIG. 2.
Penicillin metabolites.

Similar reactions occur with the semisynthetic penicillins. Penicillin metabolite antigen can also form *in vitro*. Penicillin metabolites formed spontaneously in solution can polymerise or bind proteins involved in the manufacturing fermentation process to form antigens.[4,11,14] Current manufacturing procedures remove most but not all potential carrier molecules.[4,11] Use of freshly prepared drug will decrease the incidence and severity of adverse reactions.[14]

The reason why antigen formation, a pathological immune response, and allergic reaction occur in only some exposed patients is unknown. Drug allergy is likely to have multifactorial causation involving genetic heritage, individual susceptibility, the variables of drug administration and concomitant disease.

Factors determining risk

Genetic

There is familial predisposition to drug allergy, which in mice has been shown to be unrelated to MHC alleles.[6] The incidence of drug allergy is not increased in patients with atopy, however,[2,4,7,8,15] but anaphylaxis, if it occurs, tends to be more severe.[2]

Individual predisposition

ADRs to all drugs are 3 times more common in patients with a previous history of penicillin allergy.[12] The risk of a β-lactam allergic reaction is 4 - 6 times higher in patients with a previous history of penicillin allergy but will still only occur in a minority of these patients. Those at risk cannot be reliably identified in advance. Accurate assessment of history is difficult, and non-allergic drug reactions are often misdiagnosed. The predictive value of a positive history is further limited by the decreased response to antigen with time.[16,17] Skin reaction positivity decreased with time in one study[18] from over 90% at 6 months after an anaphylactic reaction to 22% when tested 10 years later. The risk of anaphylaxis in patients with a history of a non-anaphylactic allergic reaction is not known.

The predictive value of a history of no allergic response to previous penicillin use is of limited value. Most serious and fatal reactions occur in patients with no previous history of allergy.[2,7,14] Previous drug exposure cannot be excluded by history alone, because the patient might be unaware of intra-uterine or environmental sensitisation by milk and aerosol.[11,19]

Drug administration

Allergy is not conventionally considered a dose-related reaction, but the intensity and duration of drug administration may determine the nature of the immune response. Sensitisation due to short-term low-dose exposure tends to cause the production of specific IgE.[4,6] Subsequent triggering of an immediate-type reaction may require a higher drug dose. There is a higher incidence of anaphylaxis after parenteral administration.[2,7] Only 6 cases of death due to anaphylaxis after oral therapy have been reported, while the risk of non-fatal anaphylaxis is less than half that for parenteral drug.[17] High concentrations of penicillin metabolites may be required for the degree of IgE cross-binding necessary for rapid mast cell activation and degranulation.

High-dose prolonged drug use tends to result in an IgG-mediated response.[4,6] The risk of serum sickness, interstitial nephritis and leukopenia increases with dose and duration of therapy. Chronic low-dose exposure to parenteral depot penicillin does not seem to increase the risk of an allergic reaction. A study of the use of prophylactic benzathine penicillin in a young population showed that anaphylaxis and rates of skin test positivity were no higher than for patients receiving single-dose therapy for sexually transmitted diseases.[20]

Age

The incidence of penicillin allergy is highest in adults and tends to decrease towards the extremes of age.[19] Penicillin and aminopenicillin are commonly prescribed for children, and the gastro-intestinal and cutaneous reactions which occur may be labelled as allergic.[15] The true incidence of allergy in children is far lower than that in adults.[15] Children are also less likely to show sensitisation on skin testing after a reaction.[15,17] Type I reactions are rare in children, even those with a history of cutaneous reactions to penicillin.[15,21]

Infection

Antigen presentation during infection may be influenced by endotoxin-induced production of tumour necrosis factor (TNF), interleukin-1 (IL-1) and other cytokines.

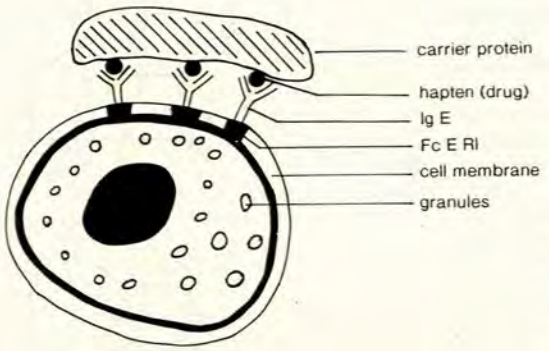
In addition, micro-organisms may release 'super-carrier' molecules capable of binding multiple drug molecules to form potent antigens.[5]

Classification of mechanisms of allergy

Accurate classification is difficult. Diagnosis is often uncertain and the responsible immune mechanism unclear. Despite the problem of overlap of mechanisms the classification system described by Gell and Coombs is still widely used.[2] The four groups are: type I — immediate hypersensitivity; type II — cytotoxic antibodies; type III — immune complex; and type IV — cell-mediated.

Type I

IgE production is a necessary but not a sufficient precondition. Although exposure to penicillin metabolite protein conjugates results in the production of antigen-specific IgE in 10 - 15% of patients receiving prolonged high-dose therapy, few of these will have type I reactions on re-exposure to antigen.[22]



CARRIER –HAPTEN CONJUGATE BINDING
CAUSES RECEPTOR CROSS LINKING

FIG. 3.
Mast cell.

The IgE antibody response to antigen is idiosyncratic and cannot be predicted or explained in an individual by currently available methods. B-lymphocyte class-switching from IgM and IgG to IgE production may be the principal aetiological step. This is regulated by interleukin-4 (IL-4) produced by helper T lymphocytes (T_H). A subgroup of T_H cells have receptors for the constant region of IgE (Fc E R) and synthesise and release IgE-potentiating and inhibiting factors.[9] IgE isotype switching and activation of IgE memory cells is enhanced by T_H2 produced IL-4 and suppressed by T_H1-produced prostaglandin E interferon-α_2 and interferon-γ.[9] A better understanding of determinants of the T_H2:T_H1 ratio may provide the key to the management of acute allergic reactions.[6]

Re-exposure to the antigen may cause IgE-mediated mast cell and basophil degranulation. Degranulation requires cross-linking of the high-affinity specific IgE Fc receptor I (Fc E RI) on mast cells and basophils. Each basophil or mast cell has approximately 10^5 Fc E RI molecules.[10] Cross-linking occurs when the antigenic determinants of the hapten bound to the carrier molecule bind drug-specific IgE on the mast cell surface. Multivalent carrier molecules (multiple penicillin molecules bound to carrier molecule) cause Fc E RI aggregation in the cell membrane and cell activation[6] (Fig. 3). This occurs with cross-linking of less than 1% (< 100 molecules/cell) of total surface IgE.[10] Anti-IgE antibodies and mitogen can also activate the Fc E RI.[10]

Cross-linking initiates a complex series of membrane and intracellular events culminating in degranulation and release of mediator molecules.

Activated complement components C3a and C5a activate mast cells directly by binding distinct surface receptors. Morphine, dextran, mannitol and contrast media (hypertonic solutions) and polylysine also cause direct mast cell activation.[8,10] The mechanism of NSAID-induced anaphylaxis is uncertain.[8]

Mast cell and basophil activation cause an immediate, intermediate or delayed-onset reaction of a generalised or localised nature. Mast cell degranulation occurs rapidly after activation and is not cytotoxic to the degranulating cell.[10] The primary (granule-stored) mediators in the human are histamine, eosinophil and neutrophil chemotactic factors, proteases and heparin.[6,10] Histamine, which comprises 10% of granular content by weight,[6] is the fastest-acting and most important mediator[6] causing bronchoconstriction, vasodilation, increased vascular permeability, and goblet cell mucus secretion.[6,7] Vasodilation may be mediated by histamine-induced release of nitric oxide from endothelial cells.[7] Activated mast cells also synthesise and release TNF, IL-1, 2, 3, 4, 5 and 6, prostaglandins, leukotrienes and granulocyte macrophage colony-stimulating factor.[6,7,10] TNF and IL-1 may have a role in the causation of the shock of acute anaphylaxis. Cytokines are the principal mediators of the intermediate and delayed inflammatory responses.

The effect of mast cell/basophil activation depends on the number and anatomical site of effector cells. Generalised activation with release of mediators into the circulation causes anaphylaxis, the least frequent but most serious of all ADRs.[7] Symptoms begin within minutes, peak at 15 - 30 minutes and resolve within hours.[7] Biphasic reactions do occur but are rare.[8] Localised mediator release results in exanthems, urticaria, bronchospasm and hayfever. Urticaria and pruritic skin reactions are the most common manifestation of IgE-mediated allergy.[23]

Type II

Antigen is formed after nonspecific adsorption of drug onto cell membranes by binding to cell membrane protein.[6] This may evoke immune sensitisation with production of specific IgG antibodies. Cell-bound antibody can activate, complement and bind the Fc receptor of macrophages, neutrophils, platelets, eosinophils, and the large granular lymphocytes, i.e. NK and K cells.[9] Activation of these cells may result in a cytotoxic response.

Type II reactions are a rare but important cause of haemolysis with use of penicillins and cephalosporins. Cephalosporins have lower affinity for red blood cell binding and cause fewer reactions.[12] The incidence is markedly increased in renal failure, suggesting a dose-related mechanism.[3]

Penicillin-specific antibodies reacting with tubular basement membrane occur in patients with interstitial nephritis.[3] An aetiological role has not been established and this may be an epiphenomenon.

Type III

Prolonged exposure to high-dose intravenous penicillin frequently causes the production of penicilloyl-specific IgG.[4] Immune complexes formed are usually efficiently cleared by the reticulo-endothelial system. Failure of clearance may result in deposition of immune complexes in basement membranes with activation of complement and/or a cellular immune response[9] resulting in rash, vasculitis, nephritis, arthritis and haemolysis.[3] The clinical spectrum of disease ranges from mild exanthems to life-threatening serum sickness.

Type IV

This type of reaction usually occurs when drug binding to skin protein elicits a cell-mediated immune response.[12] Severe clinical problems are rare. Reactions may complicate frequent skin exposure to drugs and are an occupational hazard for nursing and pharmacy staff.

Fixed drug reaction may be a type IV immune response.

Other reactions

Procaine penicillin use may be complicated by an acute reaction characterised by a feeling of impending doom, anxiety, violent and psychotic behaviour, seizures, vertigo and tinnitus, hypo- or hypertension, tachycardia, cardiovascular collapse and sudden death. This is due to toxic and/or embolic effects following inadvertent intravenous entry of the drug suspension.[2,24] Procaine penicillin has low water solubility (1:150

wt/wt) and in blood forms 5 - 100 μm aggregates which cause pulmonary and cerebral embolisation.[24] The procaine content of procaine penicillin (6%) is sufficient to cause neuro- and cardiotoxicity.[24]

The duration of clinical features does not usually exceed 15 minutes. Incidence is 1 - 3/1 000 injections and risk increases with dose.[24] Distinction from generalised anaphylaxis is essential because management is supportive and the use of adrenaline can be dangerous.[11]

Aminopenicillins may cause a maculopapular rash, probably due to the di-amino-acyl side-chain[2] and not associated with IgE-mediated β-lactam allergy.[12] The mechanism of this reaction is uncertain. Aminopenicillin-specific IgM and IgG are found in some patients[3] but have not been demonstrated to have a role in the reaction, which may be toxic in nature.[14]

The risk of rash is markedly increased (> 90%) in patients with acute infectious mononucleosis given aminopenicillins.[14] Patients with chronic renal failure, gout and lymphocytic blood dyscrasias are also at increased risk.[3]

Penicillin is well tolerated in these patients on re-exposure,[14] but the latter may be dangerous because definite initial differentiation from a penicillin reaction is not possible.

Epidemiology

The incidence of allergic reactions to drugs is difficult to determine. There is a bias towards reporting the severe and especially the fatal events, together with inadequate reporting of adverse events from the developing regions of the world where the penicillins are extensively used. With a few notable exceptions, most studies are from the developed world. Many date from the 1950s and 1960s when there was a lesser tendency to discriminate between ADRs of allergic and non-allergic cause.

Up to 5% of the general population[3] and up to 20% of hospital patients claim a history of penicillin allergy.[25] Current data suggest that its true overall incidence is between 0,7% and 8%.[2,10] The most common allergic manifestation is urticaria and about half of all allergic reactions are dermatological.[13,23]

Generalised anaphylaxis occurs in 0,004 - 0,015% of treatment procedures.[2,3] Less than 50% of reactions are severe[3] and 10% are fatal (1/50 000 - 100 000 treatment procedures);[1,2,3,18] 88,7 - 96% of fatal anaphylactic reactions occur within 1 hour of drug administration.[2,3,18] Over half of the deaths due to penicillin-induced anaphylaxis occur in patients with no previous history of penicillin allergy.[14]

Cross-reactivity does occur between penicillins and cephalosporins. While primary cephalosporin allergy is rare,[26] penicillin-allergic patients receiving first- and second-generation cephalosporins have a 4 - 6 times higher incidence of allergy, which is reported to range from 8% to 16%.[1,3,7,18] Some cephalosporins (e.g. cephalothin) tend to cause more allergic reactions, possibly because of reactions to side-chain epitopes.[7] The contamination of early preparations of cephalosporins by small amounts of penicillin synthesised by the cephalosporidium mould may have been a reason for the higher incidence of cross-reactivity initially reported.[12] The extent of cross-reactivity between penicillins and third-generation cephalosporins is controversial and clinical experience suggests that it is uncommon. Some studies have suggested that there is no increase in the risk of allergy to third-generation cephalosporins in penicillin-allergic patients.[1] However, the antigenic properties of the shared β-lactam ring (Fig. 4) suggests that some degree of cross-reactivity is likely. Half of the few recorded cases of anaphylactic reactions to third-generation cephalosporins have occurred in patients with a previous history of penicillin allergy.[18] The carbapenems have significant immune cross-sensitivity with penicillin.[2,7]

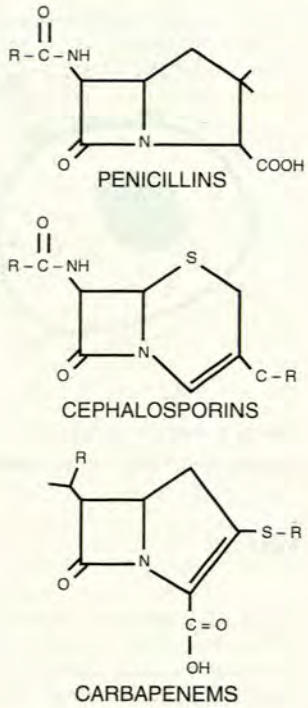


FIG. 4.
Beta-lactam structure.

Testing for allergy

The only certain test for drug allergy is rechallenge. This can be dangerous and is unethical unless use of the drug is essential. Alternative tests for drug allergy are currently unsatisfactory. Allergenic metabolites and the mechanism and determinants of the allergic response are unknown. Penicillin anaphylaxis is believed to be due to the minor determinants, but the metabolite responsible for cephalosporin allergy is not known.

Skin tests

Skin tests assess the cutaneous response to intradermal injection of penicillin metabolites. The method is not universally accepted as reliable and should only be done by an experienced practitioner.[11] Optimal results require the use of both major and minor determinants.[2] The major determinant, conjugated preparation benzylpenicilloyl-polylysine (20 lysine and 12 - 15 penicilloyl groups per conjugate complex) (PPL), is produced commercially but is not freely available in South Africa. The more important minor determinant mixture (benzylpenicilloate — a mixture of benzylpenilloate and benzylpenicilloylamine) (MDM) is an unstable solution which cannot easily be prepared in the required conjugate-linked multivalent form.[2,18] MDM is commercially available in Europe but not the USA.[18] Benzylpenicillin, hydrolysed metabolites and spontaneous degradation products occurring in solution are used as MDM substitutes. Testing with only the major determinant will result in failure to detect 5 - 10% of positive skin tests.[2,12]

Skin testing has an inherent risk. Slow diffusion of PPL from injection site has been implicated in systemic reactions, which occur in less than 1% of patients tested.[3] At least 3 deaths after skin testing have been reported.[3,18]

Skin testing may give a false-negative result if performed while the patient is taking antihistamines (H_1-antagonists), tricyclic antidepressants or sympathomimetic drugs[2] or during serious illness.[12]

Results of large studies suggest a high negative and a lower positive predictive value. Of patients with a history of a previous penicillin reaction, 7 - 35% will have positive skin tests using PPL and an MDM preparation. Children tend to have a lower positive response rate than adults.[7] Of skin test-positive subjects, 9 - 70% will have an allergic reaction on penicillin challenge.[2,18] The wide response range is due to the small number of subjects in each study, referral bias and variation in populations and testing methods used.[18] The positive predictive value in patients with a positive history is 50 - 70%. This implies that at least 30% of patients with penicillin-specific IgE antibodies, as detected by skin testing, do not react to penicillin.[22]

Of history-positive, skin test-negative patients, 1 - 3% will have an allergic response. In most this will be mild and limited to the skin.[2,18] A negative skin response to PPL and MDM effectively means that there is no increased risk of an immediate life-threatening allergic reaction.[3] The negative predictive value for penicillin skin testing in patients with prior history of penicillin allergy is 99% for reactions of clinical significance.[22]

There is no role for skin testing in patients with no previous history of penicillin allergy. The negative predictive value of a negative skin test in a patient with no history of allergy is 99,5%, which is not significantly different from the negative predictive value of a negative history.[22] A strongly positive reaction on skin testing for penicillin allergy has a positive predictive value of between 6% and 10% in patients with no previous history of allergy.[3,18] Use of the skin testing will not significantly decrease the risk of an allergic reaction to penicillin.

Skin tests should only be done at the time that penicillin therapy is required. Testing cannot be performed in anticipation of future use because the test is immunogenic and sensitivity can change with time. Results are not considered valid for more than 24 hours.[12] Penicillin skin tests do not reliably predict the risk of a cephalosporin reaction,[27,28] for which there are no validated skin tests.[12]

Radio-allergosorbent test (RAST)

The RAST is used to detect penicilloyl-specific IgE in serum. There are no generally available tests for minor determinants.[12,15] Results correlate well with those of skin testing.[2,3] False-positive results can be due to non-specific binding associated with high serum IgE levels and blocking antibodies can cause false-negative results.[2] The major advantage of the RAST is safety, since the patient is not exposed to penicillin metabolites, and the major disadvantage is delay before results are available.

Other *in vitro* tests

Measurement of **antigen-specific IgM and IgG** is only of value in the investigation of drug-related thrombocytopenia, haemolytic anaemia and granulocytopenia.[2]

In **basophil degranulation tests** histamine release is measured after exposing fresh leucocytes to antigen *in vitro*. The assay is laborious, of limited availability and less valuable than skin testing or RAST.[2,12]

Lymphocyte transformation and macrophage inhibition factor assays are slow and laborious and have poor reproducibility.[2,13,29] They have little clinical value.

Histamine, prostaglandin D_2 (PGD_2) and tryptase levels. Serum histamine and PGD_2 and their urinary metabolites are elevated for a short period after an episode of anaphylaxis. Their levels can be measured to confirm the diagnosis. Mast cell-derived **serum tryptase** levels remain elevated for a longer period and provide direct evidence of mast cell degranulation.[2,8] Levels correlate better with the clinical presentation than do those of histamine and PGD_2.[5]

Safe use of a suspect drug

The prospective assessment of individual risk of drug allergy is difficult. History-taking is a nonspecific cost-effective screening test which helps to avoid dangerous drug use at the expense of excluding the use of effective drugs which may be safe. Patients with no history of pencillin allergy can be treated with pencillins without further investigation. No currently available tests will increase the safety of use. Awareness of the risk of anaphylaxis in this group may save lives, however, and parenteral penicillin should never be administered if trained staff and basic resuscitation equipment are not available (Fig. 5). Patients with a history of pencillin allergy should ideally not receive penicillin, because the only certain test of safety is rechallenge, which is intrinsically dangerous.[15] Cephalosporins should only be used when necessary and where immediate resuscitation is possible.[11,14]

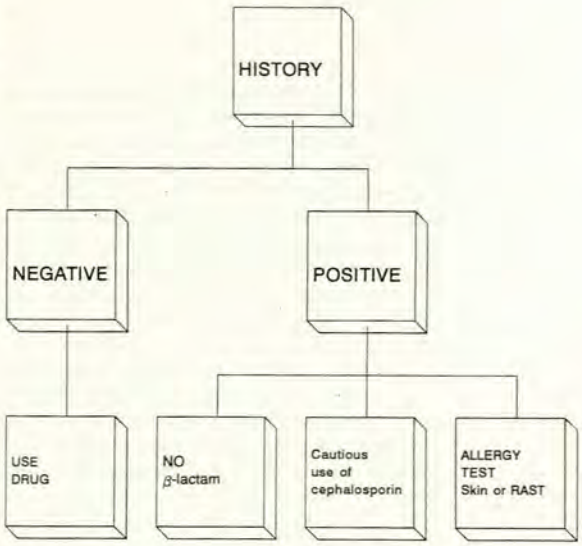


FIG. 5.
Safe use of a suspect drug.

In certain circumstances the need for a pencillin is sufficient to warrant further investigation of the safety of use. The indication may be 'absolute', as in *Streptococcus viridans* endocarditis, neurosyphilis, syphilis during pregnancy or listerial meningitis, or 'relative', as in meningococcal meningitis and rheumatic fever prophylaxis.

The recommendations for testing and drug use are not well defined. Sensitivity should be assessed by skin testing or a RAST. If this is negative, penicillin can be started at full dose under careful observation (Fig. 6).

If tests are positive and therapy is still considered essential, the patient should undergo desensitisation in an intensive care unit. Protocols for this procedure are well described.[2] Drug administration is started at a very low oral dose with cautious increases to full-dose

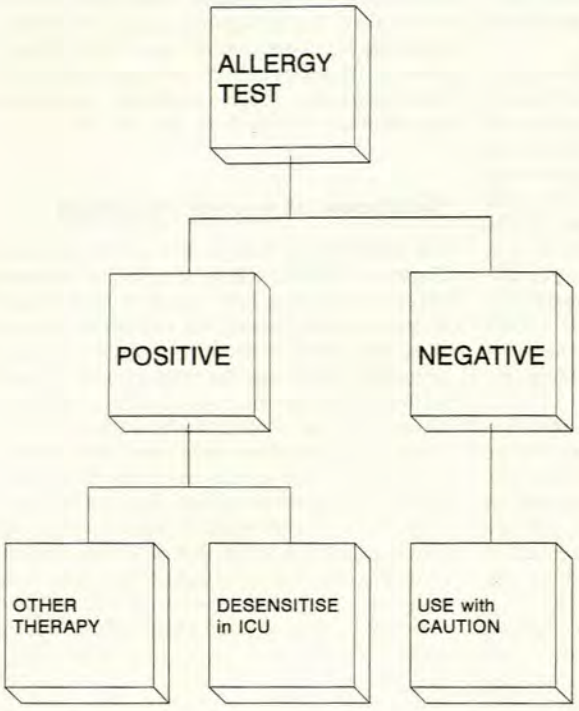


FIG. 6.
Sensitivity tests.

therapy. The mechanism of desensitisation is uncertain. Incremental exposure may result in gradual and subclinical mast cell degranulation; univalent antigen complexes may bind IgE and block cross-linking and degranulation;[4] and the slow formation of low-valency antigens may cause gradual cross-linking, degranulation[5] and mediator depletion.[3] Therapy must be continuous to maintain immune non-reactivity.

Premedication with antihistamines and/or corticosteroids is of no proven value[2] but is advised by some authors.[12] About one-third of patients will experience a transient allergic reaction, which is usually mild.[2]

After antigen exposure ceases, mast cell reactivity and clinical sensitivity return within 1 - 3 days.[5]

Generalised anaphylaxis requires immediate management with supportive therapy. The only therapeutic drug of proven efficacy is subcutaneous adrenaline, which is a physiological antagonist of mediator effects and also acts to stabilise mast cells and basophils.[7] Corticosteroids have no effect for at least 1 hour and there is no proven role for antihistamines.[3]

Conclusion

Allergic reactions are a well-publicised and important but relatively rare complication of drug use.

The allergic reaction cannot be reliably predicted and a conservative approach to patients with a history of allergy is prudent. Allergy should be anticipated in all patients who are treated with penicillin. Generalised anaphylaxis is a potentially fatal reaction that can be treated successfully.

The author wishes to thank Dr A. Robins for his help in preparing the manuscript.

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