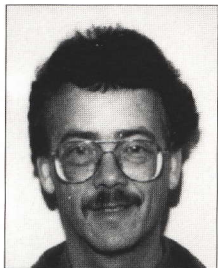


Drug Allergy



Curriculum Vitae

Prof Potter studied in Cape Town and is currently Associate Professor and Acting Head of the Department of Clinical Science and Immunology at his old alma mater. His special interests are Indigenous South African allergies, Complement Deficiency and Inflammatory Markers of Asthma, and Beta-2 Receptors. He is Chairman of the Allergy Society of SA and also a member of the House of Delegates of International Association of Allergology and Clinical Immunology. Prof Potter has published many articles in international journals. He is married and they have four children.

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Summary

Although there is a variety of side effects produced by drugs, true allergic reactions occur in only about 5% of all treatments. These are described, the risk factors highlighted and the treatment approaches given.

Incidence

Given the variety of side effects produced by drugs, it is difficult to establish the incidence of truly allergic reactions. About 15% of all hospitalised patients will experience some adverse reactions to drug therapy, and it is estimated that truly allergic reactions occur in about 5% of all treatments. The incidence varies from one drug to another (eg reactions to contrast reagents and Penicillin are common whereas very uncommon for glucocorticoids).

Type of Drug Reactions

Before focussing on allergic reactions to drugs it is important to consider the different types of reactions which can occur. These have been classified as follows:

- **Non Drug Related**
 - a) Psychogenic
 - b) Coincidental
- **Drug Related**
 - a) *In susceptible subjects:*
 - i) Intolerance
 - ii) Idiosyncratic
 - iii) Allergic or hypersensitive
 - b) *In non susceptible subjects:*
 - i) Overdosage
 - ii) Side effects due to pharmacological actions (eg Tachycardia)

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- iii) Secondary to therapeutic effects (eg Herxheimer)
- iv) Drug interactions.

Risk Factors for Drug Allergy

Age is a risk factor. Allergic reactions are uncommon in children. Allergy to muscle relaxants and to chymopapain is more common in females. Atopy is only a risk factor for allergy to a few drugs (eg chymopapain). Intravenous administration increases the risk of immediate allergic reactions. Previous history of any reaction to a drug is a very important risk factor. Drug allergies are more common in patients with AIDS and cystic fibrosis. In some cases there is a familial history of drug allergies.

General Features of an Allergic Drug Reaction

- Allergic drug reactions typically occur at low concentrations of the drug.
- There is often a history of no previous reaction to exposure to the drug.
- The allergic reaction to the drug does not resemble pharmacological actions of the drug.
- Symptoms occur rapidly on readministration of the drug and subside within 3-5 days of discontinuance of the drug.
- The drugs most commonly associated with allergic reactions are penicillins, sulphonamides, sulphonylurea hypopycaemics, ACE inhibitors, Thiazide diuretics.
- The clinical manifestations of Type I drug allergies generally fall into three categories:
 - a) General – anaphylactic shock
 - b) Cutaneous – urticaria, oedema or other skin reaction.
 - c) Respiratory – bronchospasm.

Immunological Basis for Drug Reactions

Clinical reactions to drugs are conveniently classified by the underlying Gel and Coombs immune mechanism.

1. Type I: Immediate Reactions

These reactions may result in anaphylaxis, urticaria and angioedema and occur within 30 minutes of drug administration. Penicillin is the most common cause of a true Type I IgE mediated drug allergy.

Immediate reactions may also occur via non IgE mechanisms following exposure to Radio-contrast media, aspirin, local anaesthetics and opiates such as morphine and codeine. These agents cause direct histamine release from mast cells.

2. Type II: Reactions

These reactions are due to cytotoxic antibodies binding to drug-hapten-tissue proteins and occur with the drug induced Coombs-positive haemolytic anaemias and thrombocytopenias. Interstitial nephritis may be induced by Methicillin and phenytoin sodium due to the induction of anti-tubular basement membrane antibodies.

3. Type III: Reactions

Penicillin is the most common cause of a serum sickness-like syndrome which results from immune complex deposition and manifests as maculopapular skin reactions, fever, joint pain and lymphadenopathy. Sulphonamides may induce a hypersensitivity angiitis or vasculitis. Fever may be the sole manifestation of a Type III drug reaction.

Difficult to establish difference between allergy and side effects of drugs

True allergic reaction to drug therapy is 5%

4. Type IV: Reactions

These usually result from delayed hypersensitivity to topical drug applications. The preservatives such as the parabens may also cause sensitivity. Interstitial pneumonitis associated with gold therapy is another example.

Diagnosis of Drug Allergy

The history is important. Except for Type I anaphylactic reactions, it is not uncommon for a period of 7-10 days to lapse before symptoms appear. Although symptoms should subside on discontinuance of the drug, symptoms from depot drugs may persist for a long time. Occult sources of continued drug exposure may also be important.

Because most drugs are simple chemicals they are not immunogenic. They need to complex with proteins to become immunogenic and this is also necessary for testing purposes.

1. Skin Tests

These are the main tests for drug allergy testing but there are problems with interpretation. If certain drugs are too concentrated they may cause false positive reactions. Reliable skin prick testing may be performed with Penicillin, toxoids, antisera, insulin, ACTH and egg protein vaccines. Patch tests are of value in diagnosing contact dermatitis to topically applied drugs, but are of no use in evaluating allergic reactions to oral or injected drugs.

2. Laboratory Tests

Laboratory tests are available for several drugs. RASTS are also available for alcuronium, suxamethonium, chymopapain and insulin.

Recently the application of lymphocyte transformation tests to confirm certain allergies has shown to be of value in assessing phenytoin reactions, nitro-furantoin in pulmonary infiltrates and antituberculosis drug reactions.

3. Direct Challenge

Because of the potential morbidity and possible mortality, direct challenge is not justified. Incremental skin testing however may be performed by experienced clinicians under controlled conditions in hospital where the drug is considered to be essential and alternatives are not available. It is possible to desensitise patients to drugs such as Penicillin but this should only be done in an ICU by an experienced physician in view of the inherent risks associated with this procedure.

Approach to Treatment

- Discontinue the drug. This is often all that is required.
- Treat the symptoms of anaphylaxis, urticaria, asthma or contact dermatitis.
- Corticosteroids are necessary if serum sickness or exfoliative dermatitis occurs. They will also hasten recovery from vasculitic, haematological or pulmonary vasculitis.

Allergy to Penicillin

a) Incidence

2% of all treatment will have systemic reactions. Of these 4% will have urticaria and 0,2% will have anaphylactic shock with a 0,02% mortality. Atopy is not a risk factor and mean age is 20-49 years.

b) Types of Reactions

Reactions may be *immediate*

Age is a risk factor

Allergic reactions

uncommon in children

There seems to be a familial history of drug allergies

(within 1 hour) and these manifest as anaphylaxis, urticaria, angioedema, bronchospasm.

Accelerated Reactions (1-72 hours) manifest mainly as *Urticaria*, but may manifest as erythema multiforme, a maculopapular rash or serum sickness.

Late Reactions (after 72 hours) usually manifest as morbilliform rashes or fever, but also serum sickness, recurrent urticaria and arthralgia.

c) Mechanisms

Penicillin is a low molecular substance which needs to combine with protein to become immunogenic. Major degradation products of Penicillin are the BPO (Benzyl penicilloyl) haptenic groups: *The Major Antigenic Determinant*. One can bind Benzyl penicillin to polylysine synthetically to form Penicilloyl-polylysine which is **Non Immunogenic** but can be used to identify Penicilloyl specific IgE by skin test. (Marketed as Pre-Pan). The *Minor Determinants* are other degradation products of penicillin which are important causes of *anaphylaxis*. Minor determinants (MDM) may be prepared by diluting fresh and 2-week old Penicillin G 10 000 units/ml for skin testing purposes.

d) Testing

NB: All skin testing should be done in an emergency room/ICU setting.

- Skin tests with major and minor determinants are predictive of immediate and accelerated reactions to Penicillin.
- Skin prick tests are the first line tests and are followed by intradermal tests.
- Begin with the polylysine

penicilloyl prick tests, followed by an intradermal test.

- Follow up if negative with a MDM test at diluted concentrations 1:1000, 1:100, 1:10.
- A wheal of:
 - 0-3 mm = negative
 - 3-5 mm = equivocal
 - 5-10 mm = positive
 - > 10 mm = strong positive
- False positives occur in 27% and false negatives less than 1%. Only perform intradermal tests if prick tests are negative.
- The risk of anaphylactic reaction to Penicillin is extremely low if skin tests are negative.
- For drugs other than Penicillin G, skin testing can also be performed using diluted drugs (less than 3 mg/ml).
- **RAST** testing may be done to confirm suspected sensitivity, but false negatives do occur.

e) Management

1. Avoid Beta lactams and cephalosporins in patients with a history of allergic reactions to Penicillin.
2. Choose Macrolides or cyclines.
3. Remember that Penicillin allergy is a variable state and 70% of patients will tolerate Penicillin at a later stage. Specific skin-testing should be performed if clinical indications mandate Penicillin therapy. RAST testing will confirm sensitivity.
4. Rarely (eg in subacute bacterial endocarditis) it may be necessary to desensitise a patient to Penicillin. This can be carefully done within a few hours in ICU according to defined protocols, but should only be performed by someone familiar with the technique.

True allergic drug reactions occur at low concentrations

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