SPECIAL ARTICLE

TREATMENT OF ALLERGIC ADVERSE DRUG REACTIONS

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ABSTRACT

Allergic adverse drug reactions are unpredictable and dose-independent. The cellular events which comprise an allergic reaction cannot be effectively altered until we understand how, for instance, the provoking drug forms an immunoglobulin-like factor which releases chemical mediators of inflammation from effector cells, or how these mediators act on target tissues. Nor do we know how and why different patterns of drug allergy vary over time. The post hoc treatment of reactions is largely empirical and supportive, and depends on the type of reaction and its clinical setting. The treatment of acute severe reactions like anaphylaxis include resuscitating the patient, ensuring airway patency, injecting adrenaline i.m., setting up an i.v. infusion of a plasma expander, and injecting an antihistamine and hydrocortisone. After anaphylaxis the vital signs, the ECG, and respiratory function should be monitored in the intensive care unit; supportive drugs may be needed for 72 hours. Some other systemic disorders induced by allergic drug reactions are well defined, but their treatment is either nonspecific or highly specialised. Because disease and death due to drug allergy are becoming more frequent, clinicians must try to limit them by recording careful drug histories, using radiocontrast agents only when necessary, and prescribing drugs only when benefit will probably exceed risk. Doctors should also advise their patients against the misuse of drugs.

Key Words: Drug allergy, atopy, anaphylaxis, inflammation, risk analysis.

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INTRODUCTION

An adverse drug reaction (ADR) is a harmful, unwanted effect of a drug which occurs at therapeutic dosage. An 'allergic' ADR is usually unpredictable, and dose-independent. It derives from a drug-receptor interaction which stimulates a chain of immunological events ending in the release of chemical mediators of inflammation that produce several clinical syndromes, ranging from fever to anaphylaxis.

In general, when an ADR occurs the rational response is to stop the drug ('dechallenge'), predict the risks of future dosing with the drug, and, if the risk exceeds future benefit, avoid the incriminated drug. These guidelines apply to allergic ADRs, but because of the variation of individual patient response over time, we cannot rigidly avoid certain drugs like penicillin, when they are needed to save life. Here lies the nub of the problem facing the physician, who has to decide drug policy for the patient who has had a serious allergic ADR. But before we can rationally advise our patients we must consider the scope of this problem at the systemic, tissue and cellular levels.

In particular we must assess the risk of a severe ADR. A patient in a general hospital ward receives, on average, five different drugs in five days' stay (1) (& unpublished observations), some of which neither the patient nor his doctor recognises as drugs. It is hardly surprising that about ¼ of such patients experiences one or more ADRs, some of which are allergic in type (2). Of these allergic ADRs about 1/100 is a severe reaction where the risk exceeds the putative benefit to the patient, but fortunately only about 1/1000 to 1/3000 threatens life (1-3).

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CLINICAL CHARACTERISTICS OF ALLERGIC ADRs

Certain clinical features of allergic ADRs are distinctive. Allergic ADRs are called 'Type B, or bizarre (1, 3). Thus they are different from the expected pharmacological action; clinically impossible to predict (usually); the reaction is significantly delayed after the first exposure; typically, rechallenge is rapidly followed by the reaction; small drug doses may produce severe effects; stopping the drug may sometimes settle the ADR; a small fraction only of all the subjects exposed to the offending drug are affected. The clinical types of allergic ADR, shown in Table 1, range from anaphylactic shock, a medical emer-

gency, to urticaria. Some mild and self-limiting reactions like thrombocytopenia are never detected.

Table 1:
Clinical syndromes representing systemic forms of allergic adverse drug reactions

Anaphylaxis: generalised ('anaphylactic shock')
localised (urticaria, diarrhoea, etc)

Anaphylactoid reactions
Angio-oedema
Fever
Serum sickness
Systemic lupus erythematosus
Acute or chronic active hepatitis
Acute interstitial nephritis
Alveolitis
Haematological syndromes
Cutaneous syndromes

DETERMINANTS OF RISK

The risk determinants of allergic ADRs comprise the drug, the patient and the primary disease. Inactive substances like the excipients or vehicles of the drug formulation may evoke an allergic response, e.g. propylene glycol in injectable diazepam. The route of drug delivery also bears on the overall risk: intravenous bolus injection or infusion is the most risky. Sometimes a drug-drug interaction complicates the picture, as when allopurinol predisposes patients to ampicilin rash (4). The patient's biology is important. Women and persons under 16 or over 60 years are more prone to have allergic ADRs. Certain genetic factors may also act at the population level. For the individual the only important heredofamilial factor is atopy. The atopic person is appreciably more likely to have an allergic ADR (2, 3).

The presence in the blood of heterophile antibodies to the Epstein-Barr virus in infectious mononucleosis, and to cold agglutinins in Mycoplasma infection (to a lesser degree), increases the likelihood of a morbilliform rash after the intake of ampicillin or related semisynthetic penicillins (2, 3). Active tuberculosis, and the BCG or pertussis vaccines may each have an adjuvant effect on ADRs, perhaps by potentiating an immunological mechanism (3).

PRINCIPLES AND STRATEGY OF MANAGEMENT OF ALLERGIC ADR

Allergic ADRs, from a rash to anaphylaxis, are mediated through immunological mechanisms which are usually Types I, II or III according to Gell and Coombs (5). True anaphylaxis is mediated through 'reagin', immunoglobulin E (IgE). Irrespective of the mechanism, we empirically use certain drugs to suppress (1) the effects of the chemical mediators of inflammation released by effector cells in the target tissues, and (2) some parts of the immunological cascade. These mediators, also called autacoids, include histamine, serotonin, bradykinin, prostaglandins and leukotrienes. Their cellular actions produce clinical features like hypovolaemic shock, urticaria, angio-oedema, bronchospasm and coronary artery spasm. Drugs directed towards (1) include adrenaline to counter hypovolaemic shock and bronchospasm, and histamine$_1$ receptor antagonists to counter the effects mediated by histamine. Glucocorticoids like hydrocortisone and prednisolone act in several ways (Table 2). Anaphylactoid reactions are similar to anaphylaxis, except that their clinical and cellular features cannot be attributed to an obvious immunological mechanism.

Table 2:
Summary of different cellular actions of glucocorticoids given systemically

As a group the glucocorticoids given systemically will:

Produce anti-inflammatory effects:

- stabilise lysosomal membranes
- reduce secretion and release of mediators of inflammation
- reduce vascular permeability

- reduce vasodilatation
- reduce oedema
  Potentiate response of target tissues to catecholamines
- receptor mediated bronchodilatation, etc.
  Suppress delayed allergic reactions of Types III and IV

IMMEDIATE TREATMENT OF ALLERGIC ADR

The first step is, of course, to stop the offending drug. The next step or steps depend on the clinical severity and type of allergic ADR.

If a severe reaction with cardiovascular collapse occurs, then first resuscitate the patient and secure an airway. This step may require heart-lung resuscitation and cricothyroidotomy or endotracheal intubation.

If a generalised anaphylactic reaction ('anaphylactic shock') occurs, you must recognise this as an emergency. First, give adrenaline 0.25-1.0 mg i.m. every 15 to 30 minutes until improvement occurs (6). The dose equivalent is 0.25-1.0 ml of the 1/1000 adrenaline solution BP. The dose in children should start at 0.25 mg. The hallmark of anaphylaxis is hypotension and a rapid fall in the level of consciousness. Subcutaneous injection may produce slower recovery because of poor tissue perfusion in shock.

Next, give a histamine$_1$ receptor antagonist intravenously. Promethazine 25-50 mg injected as an i.v. bolus over 3 minutes can be followed by an i.v. infusion of chlorpheniramine. Oral terfenadine and astemizole are useful only after sedation is no longer needed. Most authorities advise also giving i.v. hydrocortisone. Although the effects of glucocorticoid treatment are delayed for some hours, they may help to suppress the actions of the autacoids. All these measures are most effective if started early.

The patient with generalised anaphylaxis may continue to have dangerous upsets for several days. These disorders include myocardial ischaemia, airflow obstruction, and repeated vomiting. So it is best to observe the patient in a medical intensive care unit, monitoring the forced expiratory volume as well as the standard vital signs. Repeated doses or a continuous i.v. infusion of hydrocortisone and chlorpheniramine may be needed for about 72 hours after the first symptom.

If angio-oedema is found, give a rapidly tapering course of glucocorticoid (i.v. hydrocortisone or oral prednisolone) over about a week. The potentially lethal feature of angio-oedema is swelling of the larynx, pharynx or tongue, or all three. Local anaphylactic reactions include urticaria and diarrhoea, which may only require symptomatic measures.

OTHER FORMS OF EARLY TREATMENT

If the guilty drug has been taken in overdose, it may

sometimes be useful to give activated charcoal orally within the first hour of ingestion, or to wash out the stomach within the first four hours. Tricyclic antidepressives and salicylates should be washed out even 8 and 24 hours after ingestion respectively, because these drugs delay gastric emptying. If the drug has a prolonged half-time of elimination from the body, it is helpful to accelerate its elimination by haemodialysis or haemoperfusion, if the drug kinetics are suitable.

The other measures which are useful early in the treatment of allergic ADRs are supportive. The longer term management is either nonspecific, or determined by the complications of the ADR, or specialised and beyond the scope of this article.

TREATMENT OF OTHER SYSTEMIC SYNDROMES

Allergic ADRs may take the form of systemic clinical syndromes other than those already discussed (Table 1). The general principles applied to these syndromes are (a) to treat the clinical disease supportively and, (b) to give a short, rapidly tapered course of a glucocorticoid systemically if the constitutional upset is severe. Most physicians choose oral prednisolone or cortisone acetate. I suggest prednisolone starting at 0.5 to 1.0 mg/kg daily and reducing this dose in 5 mg steps every 3 days to 2 weeks, depending on the patient's clinical response.

Fever is a common form of drug allergy; observation and symptomatic treatment, with or without recording of markers of inflammation in the blood and urine may suffice. In drug-induced lupus erythematosus you should monitor the patient clinically and using the erythrocyte sedimentation rate. A nonsteroidal anti-inflammatory drug like ibuprofen may be given for mild problems like arthritis. A short course of glucocorticoid may be needed for the same indications as in idiopathic systemic lupus. Similar remarks apply to serum sickness, in which an H_1 receptor antagonist may help to control arthralgia.

Acute hepatitis or chronic active hepatitis is sometimes seen, notably with drugs like methyldopa, androgens and certain cytotoxic agents. The treatment is supportive and standard. Acute interstitial nephritis is the usual form of kidney damage due to drugs like the aminoglycosides and captopril. Here treatment, where clinically indicated, comprises oral prednisolone or i.v. hydrocortisone at standard anti-inflammatory doses; the place of high dose methylprednisolone is under debate. Alveolitis, usually associated with bleomycin, busulphan, nitrofurantoin and amiodarone, is treated along similar lines. The haematological syndromes induced by drugs, ranging from thrombocytopenia to agranulocytosis and aplastic anaemia, are best treated by specialists along conventional lines. The same remarks apply to the cutaneous syndromes.

CELLULAR MECHANISMS OF DRUG ALLERGY

In general, once an allergic ADR starts it is hard to interrupt, and hard to confirm by simple tests, to reproduce, and therefore to study experimentally. We cannot modify the cellular events which produce the clinical problems because we do not know, at the molecular level, how the following interactions occur. The provoking drug combines with a protein or peptide (the hapten) to form an immunoglobulin-like compound. The hapten or complex triggers the production of immunoglobulins or 'anaphylotoxins' (3). Then intermediary substances release several mediators of inflammation from effector cells, including mast cells and basophils in the target tissues (3, 6). Finally, the mediators bind to target cells to produce the many different clinical effects observed.

RECHALLENGE TESTS

The different degrees and patterns of allergic reactions in different persons, and both the variation between persons and the variation in individual reactions over time, show that unknown factors modulate the basic events in the target tissues. It is hard to test many of our concepts of drug allergy for the following reasons.

Rechallenge carries small but definite risks. For instance, intradermal or even prick skin tests with 'purified' extracts have sometimes caused generalised anaphylaxis. So such experiments must be carried out under controlled conditions on selected patients who have experienced only simple ADRs, like fever or a rash, linked to clinically important (i.e. needed) drugs. As with desensitisation of patients against bee venom, for instance, these experiments must be done by experienced doctors who know advanced life support, and who have life-saving drugs to hand. The results of rechallenge tests may not be reliable because of the variation of clinical responses over time. Studies of potentially lethal disorders like anaphylaxis, angio-oedema, or agranulocytosis pose ethical problems.

IMPORTANCE OF RISK ASSESSMENT

It is clear from the above that the immediate treatment of allergic ADRs is empirical and hard to evaluate by experiment, and ultimately depends on 'risk analysis' to guide clinical judgement. The effective long term management of allergic ADRs should therefore comprise measures to (1) prevent the event itself ('primary prevention') and (2) avoid recurrence of the event ('secondary prevention'). These measures themselves mean that doctors must learn how to assess and handle risks realistically.

All working doctors take risks, whether knowingly or not. Each time you decide whether or not to apply an investigation or treatment to your patient, you should knowingly balance the risks of injury to your patient against the likelihood of benefit.

SECONDARY PREVENTION

Severe allergic ADRs are uncommon. For instance, the incidence of agranulocytosis due to carbimazole has been estimated at 1 per 3040 in a case-control study in a population of 23 million persons in Europe (7). Similarly the incidence of true IgE-mediated anaphlyaxis due to penicillin, the commonest provoking drug, is about 1/2000 treated patients, with about 1/500000 patients dying from the reaction (8). So we may reasonably conclude that properly indicated treatment with carbimazole or the penicillins is usually justified without pretreatment tests. However, not everyone agrees with this statement.

In some unusual circumstances, such as severe anaerobic myositis, penicillin should probably be given despite a history of allergy (9). A high proportion, about 85%, of patients with minor penicillin-related allergic ADRs will tolerate repeat treatment with penicillin (10). In general, patients who have a history of drug allergy or atopy must be managed with extra care.

Severe allergic ADRs like bone marrow hypoplasia cause severe disability or death. Minor allergic ADRs may precede life-threatening ones. Because we do not know the molecular mechanisms of allergy and ADRs, any treatment is an incomplete attempt at salvage. Finally, as drug treatment becomes more widely accessible, the frequency of drug allergy will increase. What, then, can we do? The health care records of affected patients must be clearly and carefully flagged. Community alert systems like Medik Awas help to a limited degree. Uninves-

tigated reporting of ADRs deprives some patients of access to some useful drugs.

Rarely, those who have had allergic reactions to penicillin may need desensitisation, if no other antibacterial is appropriate.

DESENSITISATION TO PENICILLIN

If a penicillin is needed for overwhelming bacterial infection and no other bactericidal drug is available, then you might have to desensitise the known 'sensitised' patient to penicillin. This means raising the patient's threshold for producing IgE in mast cells and basophils. The procedure does not evoke IgG blocking antibodies. An example of a desensitisation scheme is shown in Table 3. Desensitisation is effective for up to 6 weeks only. You should supervise the patient continuously in the intensive care unit, where drugs for treating anaphylaxis are to hand. Penicillin can be given as i.v. bolus injections or, more safely, orally except for the highest test doses (11). Here it is important not to give the patient an antihistamine or glucocorticoid, as these drugs would mask any allergic reactions.

Table 3:
Scheme for supervised desensitisation to penicillin using oral phenoxymethylpenicillin followed by intravenous bolus injections of benzylpenicillin (11.12).

Start with a dose equivalent to benzylpenicillin 10 units (0.1 ml of benzylpenicillin solution 100 Units/ml)

Leave 20 minute intervals between doses

Give further doses in graded fashion as follows:-

20	50	100	units
200	500	1000	units
2000	5000	10000	units
20000	50000	100000	units
200000	500000	1000000	units

Give oral doses up to 100 000 units, and then give the last three doses intravenously.

PRIMARY PREVENTION

The widespread consumption of an ever widening range of drugs in our urban society means that a certain incidence of ADRs is unavoidable. However, doctors have a duty to limit the amount of injury due to the wrong use of drugs. What can you do here?

First, avoid those circumstances of known risk for drug allergy, e.g. record a careful drug history from every patient. Second, investigate your patients rationally: do tests with exogenous substances only when the value of the information obtained exceeds the risk to your patient. The English physician A.L. Cochrane exhorted his trainees to ask themselves always: 'What would you do if the test yields a positive result, and what would you do after a negative result? If your answers are similar, don't do the test!' Third, prescribe drugs rationally, that is, give drugs to patients only when benefit significantly exceeds risk. Last, you should educate your fellow doctors, patients, and the general public against the misuse and abuse of drugs.

Ponder, then, these lines: 'Any man's death diminishes me/Because I am involved in Mankinde/. . . And therefore never send to know/ For whom the bell tolls:/It tolls for thee.' (From Devotions XVII, by John Donne (1571-1631).

CONCLUSION

Allergic adverse drug reactions (ADRs) and unpredictable and dose-independent. The cellular events which comprise an allergic ADR are poorly understood and cannot therefore be effectively modified or prevented. The different patterns of drug allergy may vary over time in individuals. Several systemic syndromes induced by allergic ADRs are clinically defined, but their treatment is either nonspecific or specialised. The post hoc treatment of ADRs is largely empirical. The systemic allergic syndromes may require treatment with an histamine$_1$ receptor antagonist, a nonsteroidal anti-inflammatory drug, or a glucocorticoid, or all of these. Allergic ADRs are best managed by preventing their recurrence and preventing the event itself. Because disease and death due to drug allergy are becoming more frequent, clinicians must try to limit them by recording careful drug histories, and investigating and treating patients with drugs only when benefit will probably exceed risk. Physicians should constantly warn themselves, their colleagues, and their patients against the casual use of drugs.

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