

Adverse drug reactions

Clinical assessment of drug-induced disease

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Physicians are often confronted with patients who state that they are "allergic" to a drug or drugs. Knowing which medications can be prescribed safely is therefore difficult, and care of such patients frustrating. The goal of this review is to help physicians develop management plans for patients who present with drug-induced diseases. It provides information that allows physicians to differentiate between reactions that are truly allergic in nature and those that are not immunologically mediated. Relevant information on medical history, physical findings, and laboratory tests that may be helpful in the assessment are discussed, and guidance is provided on when and if a drug may be safely readministered. Unfortunately, however, until we are able to better understand the mechanisms responsible for drug-induced reactions, our management tools will remain limited.

Reactions caused by drugs (adverse drug reactions) are defined as any noxious, unintended, and undesired effects of a drug that occur at doses used for prevention, diagnosis, or treatment.¹ Unfortunately, accurate calculation of the incidence of adverse drug reactions is difficult since most of these reactions go unreported. Despite limited accurate data, a meta-analysis of 39 studies done in the USA from 1966 to 1996 found that the incidence of severe adverse drug reactions in hospital inpatients was 6.7%. Moreover, when the occurrence of both serious and non-serious adverse drug reactions were examined together, this figure more than doubled to 15.1%.² In addition to the high occurrence of adverse drug reactions and the associated morbidity and mortality, substantial costs are incurred. One study estimated that a 700-bed teaching hospital spends US\$5.6 million on adverse drug reactions in a single year.³

Although many drug reactions are preventable, such as those associated with prescription errors, many are not. Pharmaceutical companies strive to work out the adverse-effect profile of a drug before it is marketed, but because only a limited number of select individuals are exposed to an agent before it is released, the complete range of adverse effects is not known. Therefore, since the most severe drug-induced reactions cannot be uncovered before licensing, efficient postmarketing surveillance is needed. However, even if improved surveillance is implemented, the problem will not be resolved. As more drugs are marketed and as more individuals take more drugs, the occurrence of adverse drug reactions will probably continue to increase. Therefore, better approaches must be devised for reporting and for assessment and management of individuals who present with drug-induced diseases.

Few drug reactions are truly allergic. However, patients who have experienced many adverse drug reactions commonly state that they have multiple drug "allergies" and, typically, these "drug allergies" are written all over their medical records. Understandably, physicians become frustrated because they do not know what medications can be prescribed safely. The purpose of this review is to provide feasible approaches for the management of these difficult patients.

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Classification of adverse drug reactions

Description and characterisation of drug-associated reactions can be difficult. Definitions such as "toxic", "allergic", or "idiosyncratic" reaction are often used, but in many instances these labels only confuse the situation further. The confusion stems from the fact that we know very little about the mechanisms responsible for many drug-induced reactions, especially those that are not related to the drug's pharmacological properties. Adding to the confusion is the fact that pharmacologists, toxicologists, and immunologists often use different terminology. Thus, although classification systems exist, their limitations must be realised, and they must be reassessed and modified as new mechanistic data accumulate.

Rawlins and Thompson⁴ devised a classification scheme in 1991, which continues to be the most frequently used. In their scheme, shown in panel 1, adverse drug reactions are divided into two categories: reactions that are common, predictable, and that may occur in any individual (type A); and reactions that are uncommon, not predictable, and that occur only in susceptible individuals (type B). About 80% of all adverse drug

Panel 1: Classification of adverse drug reactions

Type A reactions (predictable, common, and related to the pharmacological actions of the drug)

- Toxicity or overdose (eg, hepatic failure with high-dose paracetamol)
- Side effect (eg, sedation with antihistamines)
- Secondary effect (eg, development of diarrhoea with antibiotic therapy due to altered gastrointestinal bacterial flora)
- Drug interaction (eg, theophylline toxicity in the presence of erythromycin therapy)

Type B reactions (unpredictable, uncommon, and usually not related to the pharmacological actions of the drug)

- Intolerance (eg, tinnitus with aspirin use)
- Idiosyncratic reaction (eg, development of anaemia with the use of antioxidant drugs in the presence of glucose-6-phosphate dehydrogenase deficiency)
- Hypersensitivity (immunological) reaction (eg, anaphylaxis with penicillin administration)
- Pseudoallergic (non-immunological) reaction (eg, radiocontrast dye reaction)

reactions are type A,⁵ and for most prescription medications, this type of reaction is described in handbooks such as the *Physicians' desk reference*.⁶

Type B reactions are not dose-dependent and, except for one reaction type, are not usually related to the pharmacological actions of the drug (panel 1). They are often not discovered until after the drug has been marketed. Both environmental and genetic factors are thought to be important in the development of reactions of this type.⁷ Included in this category are drug intolerance (ie, an undesirable effect produced by the pharmacological actions of the drug at therapeutic or subtherapeutic dosages); idiosyncratic reactions (ie, uncharacteristic reactions that are not explicable in terms of the known pharmacological actions of the drug); and allergic or hypersensitivity reactions (ie, aberrant reactions that result from the involvement of one or more immunological mechanisms). Pharmacologists regard allergic or hypersensitivity reactions as being a type of idiosyncratic reaction since these reactions are unpredictable, are not dose-related, and occur in only a small proportion of the population.⁸ In contrast, immunologists and allergists tend to separate out immunological idiosyncratic reactions from those that are not immunologically mediated. For the purposes of this review, an idiosyncratic reaction will be defined as an uncharacteristic, non-immunological response to a drug that is not related to its pharmacological actions.⁵ For idiosyncratic reactions that are known or are presumed to be immunologically mediated, the term "allergic" or "hypersensitivity reaction" will be used.

Although they will not be further discussed in this review, two other drug-reaction types must be mentioned. Type C reactions are associated with long-term drug therapy and include benzodiazepine dependence and analgesic nephropathy. They are well known and can be anticipated.⁸ Type D reactions refer to carcinogenic and teratogenic effects. These reactions are delayed in onset and are very rare, since extensive mutagenicity and carcinogenicity studies are done before a drug is licensed.

Hypersensitivity reactions can be further classified into those that are mediated by drug-specific antibodies and those that are mediated by drug-specific T lymphocytes. Four specific types of reaction have been described by Gell and Coombs⁹ (immediate hypersensitivity, cytotoxic, immune complex, and delayed-type hypersensitivity), but many drug reactions do not fit into any of these categories, despite having features consistent with an immunological mechanism. Many presumed hypersensitivity reactions cannot be classified because the mechanisms responsible for them are not known. And the lack of mechanistic information is due to the fact that these reactions are uncommon, unpredictable, and not reproducible in animal models.

Drug metabolism and drug reactivity

To work out the underlying pathophysiology of drug reactions, the chemical properties of the drug and its metabolism must be analysed. Many drugs are very simple chemicals of low molecular weight, and are incapable of inducing an immune response in their native form. However, simple chemicals can induce hypersensitivity reactions when they combine covalently with large-molecular-weight compounds.¹⁰ For this covalent association to occur, most drugs must be "bioactivated" or metabolised to chemically reactive products.¹¹ Typically, drug metabolism is not detrimental to the host. In fact, it is beneficial. Metabolism is a type of detoxification process whereby lipid-soluble, non-polar

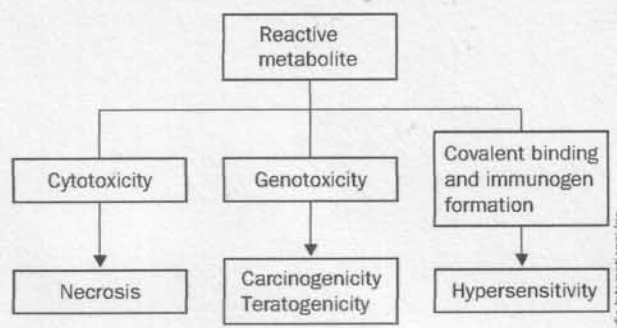


Figure 1: Role of drug-metabolising enzymes in drug bioactivation or inactivation

From reference 7, with permission.

compounds are converted to compounds that are easily excreted. Drug metabolism is usually a two-step process involving oxidation, reduction, or hydrolysis (phase I) followed by conjugation with glucuronyl, sulphate, or acetyl groups (phase II) that results in the formation of inactive compounds that are water soluble and easily excreted by the kidneys.¹²

In some instances, reactive drug metabolites that are not promptly detoxified may be formed. When this happens, the metabolite may cause direct cytotoxicity leading to direct tissue damage and necrosis; it may bind to nucleic acids to produce an altered gene product; or it may covalently bind to a larger macromolecule inducing an immune response (figure 1).⁷ Sulphonamides, for example, can be metabolised to reactive intermediates that elicit both direct cytotoxicity¹³⁻¹⁷ and immune responses through covalent binding with protein macromolecules.^{18,19}

Background information important in the assessment of drug-induced disease

Physicians are asked to assess drug reactions while they are in progress or afterwards when all clinical evidence of the event has resolved. If the patient is in the midst of a reaction, medical history, physical findings, and laboratory information can all be used to find the drug responsible as well as to help elucidate the reaction type. In many instances, however, the drug reaction has long resolved, and the physician has no objective information upon which to base a decision about whether or not to readminister the drug in question. Even here, much useful information can be obtained if a detailed history is taken.

Panel 2 outlines the information that must be obtained during the assessment of a patient who has had a drug-associated reaction. Importantly, before the hospital or clinic appointment, the patient must be advised that detailed questions will be asked. Since patients often cannot recall important details clearly, all relevant medical records should be available. Not only is this information vital to the physicians but it also makes patients less anxious, since they can become frustrated and embarrassed if they cannot recall specific details.

Sometimes it is very easy to find the cause of a presumed drug-induced reaction, especially if the patient is taking a single drug at the time. However, individuals who have several chronic diseases, such as hypertension, diabetes, and coronary-artery disease, commonly take several medications, and it can be difficult to work out which is the cause. The temporal relation between the start of drug therapy and the onset of the reaction is very helpful. A drug that has been taken for several years is unlikely to be the cause of the reaction. Another temporal consideration is that, unlike type A reactions,

Panel 2: Questions a physician should ask when assessing a patient with a suspected drug-induced disorder

- Is there any history of drug-induced reactions? If so, what were the characteristics of the previous reactions?
- At what stage during therapy did the current reaction occur?
- At the time of the reaction, what drugs was the patient taking, when were they started, and what were the doses of each?
- Had the patient been exposed to any of these drugs previously?
- What are the patient's other medical problems?
- What were the clinical manifestations of the drug-induced reaction and could these manifestations help determine which drug was responsible for the reaction?
- Were there any laboratory abnormalities that could be explained by a drug-induced reaction?
- When the drug was discontinued, did the reaction cease?

immunologically-mediated hypersensitivity reactions require a period of sensitisation of several days. Hypersensitivity reactions often do not occur during the first course of therapy, but present during subsequent courses. A confusing picture arises when a patient presents with a first-dose reaction that seems clinically to be anaphylactic. Since drug-specific IgE antibodies cannot be made instantly, another mechanism must be operative. Either the patient had been previously exposed to the drug or to a cross-reacting agent and had formed drug-specific IgE-antibodies, or the reaction clinically resembled anaphylaxis but an immune mechanism was not involved. Reactions of this latter type ("pseudoallergic") can be caused by, for example, radiocontrast media, neuromuscular blocking agents, opioids, colloid volume expanders, and some antibiotics (eg, vancomycin).²⁰

By examining the properties of the drugs themselves, useful information can be obtained. Pharmacological adverse reactions can be caused by the primary pharmacology of the drug (augmentation of the drug's therapeutic actions) or by the secondary pharmacology (an action that differs from the drug's therapeutic actions but that can still be rationalised from the known pharmacology of the drug).²¹ For β blockers, heart block and bradycardia are primary pharmacological adverse effects; bronchospasm is a secondary effect. Some factors predispose to pharmacological adverse reactions; these include drug dose, drug formulation, pharmacokinetic or pharmacodynamic abnormalities, and drug-drug interactions.²¹ Therefore, to find out whether a reaction is due to the pharmacological actions of the drug, the physician needs to know the doses of all medications, concurrent medications taken at the time of the reaction, and concurrent diseases (eg, renal failure, hepatitis) that could lead to alterations in drug excretion or drug metabolism.

Some drugs cause characteristic clinical reactions. Therefore, it is important to be familiar with the various types of adverse reactions that a particular drug may elicit. In many instances this task is not so simple, since one drug can be responsible for causing a range of reactions, some of which can be related to its pharmacological properties, and others to its immunological properties. Sulphonamides, besides causing type A reactions such as toxicity, can be associated with various other reactions that fall into the type B (unpredictable) category. These reactions, which are thought to result from direct cellular cytotoxicity or an immune-mediated mechanism, include

erythema multiforme, fixed drug eruption, urticaria, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

Almost all drugs are capable of causing numerous adverse-reaction types. Therefore, when an individual presents with a drug-induced reaction, a careful physical examination focused on the organ systems involved in the reaction should be done, and then the adverse-reaction profile of all administered drugs should be reviewed to pinpoint the most likely culprit. Several drug-reaction manuals catalogue prescription and over-the-counter medications by their adverse-reaction profile.^{22,23} These manuals can be very useful when a drug-induced reaction is known (or presumed) to be occurring, but they may be less useful when the patient is on multiple medications.

Finally, it is also important to remember that the clinical picture may not be drug-induced at all. About 50% of cases of Stevens-Johnson syndrome are drug-induced; the others are caused by infectious agents.²⁴⁻²⁶ Therefore, when assessing a patient with Stevens-Johnson syndrome, drug-induced and non-drug-induced causes must be considered. Thus, although medications can cause a multitude of organ-specific and, sometimes, systemic reactions, physicians should always consider other potential causes before concluding that the clinical abnormality is drug-induced.

Clinical approach to patients with drug-induced disease

The simplest approach to patients who present with a history of previous adverse drug reactions is probably "better-safe-than-sorry".²⁷ This strategy involves assuming that the patient has had an adverse reaction to a particular drug, and telling the patient that, in light of this drug sensitivity, he or she should avoid the drug in the future. Despite being the safest approach, it is not the most practical and it may deprive patients needlessly of important drugs. In addition, this approach is leading to a major clinical problem: the development of antibiotic-resistant organisms. One survey found that physicians tend to prescribe alternative broad-spectrum antibiotics without assessing whether or not patients with an assumed penicillin allergy are truly allergic.²⁸ This approach could be contributing to the emergence of vancomycin-resistant enterococci and staphylococci. Thus, the "better-safe-than-sorry" strategy cannot be regarded the best management approach.

Diagnostic tests for drug-induced disease

As stated previously, most adverse drug reactions are predictable (type A). These reactions are related to an agent's pharmacological properties and are well described in the adverse-reaction profile of a drug when it is marketed. In contrast, type B reactions are not predictable, nor are they common. For these reasons, it is desirable to have a diagnostic test that would allow one to predict whether or not an individual is at risk of developing a subsequent, similar reaction if the same drug was readministered. Idiosyncratic reactions and reactions due to drug intolerance will occur again if the causative drug is readministered. Therefore, of the type B reactions, diagnostic tools are useful only for hypersensitivity reactions or those that are presumed to be immunologically mediated.

General laboratory tests may be helpful for some types of drug-induced disease processes, especially when there is organ-specific involvement. Depending upon the organ system involved, one or more of the following tests may be helpful: liver-function tests, measurement of blood urea

nitrogen or creatinine, complete blood count, urinalysis, and chest radiograph if there is pulmonary involvement. Also helpful are biochemical and immunological markers that confirm the activation of certain immunopathological pathways.²⁹ Thus, depending upon the reaction type, measurement of the following may be useful: total haemolytic complement concentrations (for drug-induced immune-complex reactions that result in complement activation); antinuclear antibodies (for drug-induced lupus); and 24-h urine histamine metabolite (for drug-induced anaphylaxis).

A biochemical marker that has proven useful for disorders that involve systemic mast-cell activation is tryptase. Tryptase is a neutral protease that is stored in mast-cell granules; it exists in an α form and a β form.³⁰ Raised concentrations of α tryptase in blood indicates that there are increased numbers of mast cells—a finding that is seen in systemic mastocytosis. The β form is a measure of mast-cell activation, and concentrations are raised in mast-cell-dependent anaphylactic or anaphylactoid reactions. Therefore, β tryptase concentrations are increased for reactions resulting from drugs that cause mast-cell-mediator release via an immunological mechanism (eg, heterologous antisera, insulin, penicillin), and from drugs that cause mast-cell-mediator release via non-immunological mechanisms (eg, opiates, muscle relaxants, and volume expanders). The half-life of tryptase in plasma is about 2 h and the enzyme is not prone to rapid degradation. For these reasons, measurement of tryptase concentrations is favoured over measurement of serum histamine. Matsson and colleagues³¹ reported two cases of intraoperative anaphylaxis to anaesthetic drugs in which tryptase concentrations were raised; others have also reported increased tryptase concentrations after drug-induced perioperative anaphylaxis.³² Schwartz and colleagues³³ recommend that tryptase concentrations be obtained 1–2 h after the onset of the anaphylactic episode. Normal serum concentrations of β tryptase are less than 1 $\mu\text{g/L}$. Concentrations greater than 1 $\mu\text{g/L}$ indicate mast-cell activation, and concentrations greater than 5 $\mu\text{g/L}$ are typically seen in mast-cell-dependent systemic anaphylaxis. However, despite the usefulness of this test in assessing anaphylactic or anaphylactoid reactions, it is important to note that β tryptase concentrations can be normal if the reaction does not involve haemodynamic changes.³³

Although some specific diagnostic tools exist for the assessment of drug-induced hypersensitivity diseases, they are limited in number for two reasons. First, for many drug-induced reactions, drug metabolites or degradation products and not the native drug are responsible for the reaction. Unfortunately, the immunochemistry of most drugs, especially low-molecular-weight haptens, are not known. Therefore, without knowledge of the clinically relevant drug determinants, diagnostic materials cannot be devised. Second, in many instances, the actual mechanisms responsible for the reactions have not been elucidated, so it is not possible to choose an appropriate test. Although drug-specific antibodies can be present in a patient with drug-induced hepatitis, their presence does not necessarily mean that they are responsible for the disease process. In some instances, their appearance may represent an epiphenomenon.

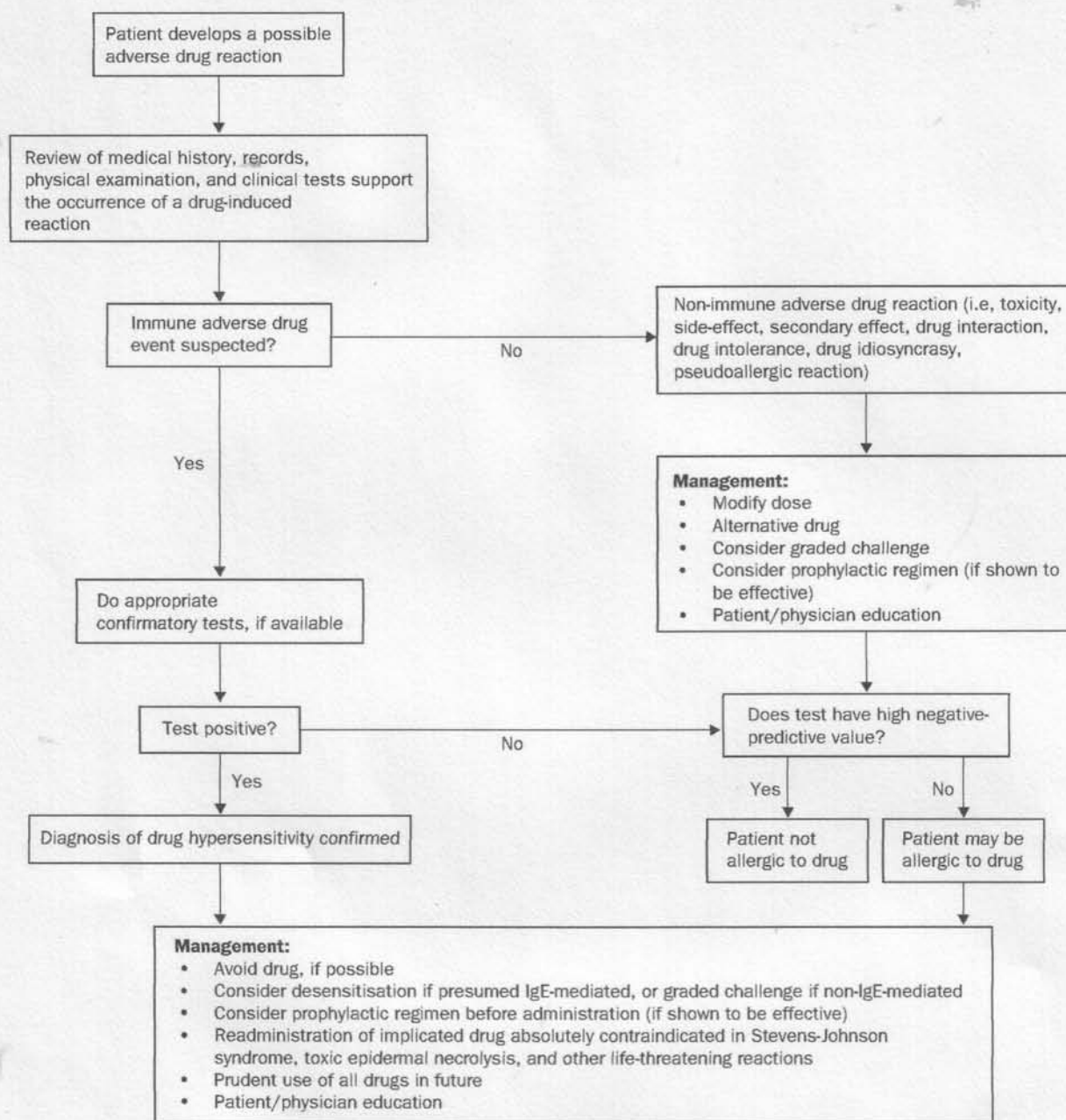
For immediate hypersensitivity reactions, skin testing can be done to find out whether drug-specific IgE antibodies exist. Their presence indicates that the patient is at risk of an IgE-mediated reaction, including anaphylaxis, if that agent were to be given again. Skin testing is especially useful for polypeptides that are

multivalent and of large molecular weight such as antilymphocyte globulin, toxoids, insulin, and streptokinase. It is less useful for small-molecular-weight agents like antibiotics because, except for penicillin, the relevant immunogenic determinants for most antibiotics have not been identified. Despite this lack of knowledge, beneficial information may be obtained if skin tests are done with non-irritative antibiotic concentrations. A positive result suggests the presence of drug-specific IgE antibodies. In contrast, a negative result could mean either that drug-specific IgE antibodies are absent or that they are present but not detectable because an inappropriate immunogen was used as the testing reagent.

Although in-vitro tests to detect drug-specific IgE antibodies to antibiotics exist, they have the same limitations as in-vivo skin tests and, in addition, they are less sensitive. Thus, clinicians must be cautioned about using these assays in the diagnostic assessment of an antibiotic-allergic individual. Some commercial laboratories specialising in allergy and immunology offer in-vitro diagnostic tests for drug-specific IgE antibodies to select antibiotics. However, the usefulness of these tests is unclear. The same problems that plague skin-testing affect the in-vitro assays as well. Lack of knowledge of the clinically relevant antigenic determinants makes it difficult to interpret a negative finding. The inability to detect drug-specific IgE antibodies does not mean that they are absent. The antibodies are just as likely to be present, but not detectable, perhaps because the antigen coupled to the test disc is not the clinically relevant one. Until more information about the correct immunogenic determinants of antimicrobial agents is generated, in-vitro assays for IgE antibodies to these agents have limited, if any, use in the diagnostic assessment of drug-allergic patients.

The tools available for the assessment of non-IgE-mediated drug-induced hypersensitivity reactions are also limited.³⁴ In addition to limited knowledge of relevant antigenic determinants and pathogenic mechanisms, the clinical relevance of the available tests must be determined. Although drug-specific IgG or IgM antibodies may cause thrombocytopenia, haemolytic anaemia, and neutropenia, there is often no correlation between the presence of these antibodies and pathogenesis. A similar lack of correlation may be seen with lymphocyte-transformation testing. A marked proliferative response induced in a drug-allergic patient's lymphocytes when they are cultured in the presence of the suspected drug indicates specific T-cell sensitisation, but whether this finding is clinically relevant is not clear.

In the past, patch testing was thought to be useful only for drug-induced contact dermatitis. However, in light of accumulating evidence that supports an immunopathogenic role for specific T lymphocytes in some drug-induced reactions, including morbilliform eruptions, fixed drug eruptions, and bullous eruptions, patch testing may have more broad applicability in the assessment of drug-induced hypersensitivity. Romano and colleagues³⁵ found that 33 of 60 patients who had maculopapular eruptions to ampicillin, amoxicillin, or penicillin showed positive delayed intradermal skin-test responses, as well as positive patch-test responses, when tested with the clinically relevant drug. Osawa and colleagues³⁶ also found that patients who had non-immediate-type drug-induced eruptions often had positive patch-test responses. Although individuals who had eczematous eruptions were more likely to have positive patch-test responses than those who had maculopapular eruptions, a large number of patients who had experienced other drug-induced systemic eruptions (erythema multiforme, erythroderma,



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Figure 2: **Algorithm for management of adverse drug reactions**
From reference 37, with permission.

fixed drug eruption) were patch-test positive as well. These exciting findings suggest that specific T cells may have a pathogenic role in several important drug-induced cutaneous hypersensitivity diseases, and that patch testing may prove to be useful in their diagnostic assessment.

Most importantly, physicians and patients must realise that, in most instances, no single diagnostic test will answer the common question, "Is the patient allergic?". Although a wheal-and-flare skin-test response to streptokinase in a patient previously exposed to this agent indicates that the patient has drug-specific IgE antibodies and is at risk for anaphylaxis if streptokinase is readministered, many drug-induced hypersensitivity responses are not this easy to assess. For many reactions, neither the immunopathogenic mechanisms nor the clinically relevant drug metabolites responsible for inducing the reaction are known. However, despite the limited number of diagnostic tools available for the assessment of patients who present with drug-induced

disease, reasonable management strategies can still be devised.

Management strategies

If a drug-disease connection has been established, and there is a need to give the implicated drug again, several options may be considered (figure 2).³⁷ For type A reactions, only minor modifications may be required before drug readministration. In the case of toxicity, provided the tissue affected has the ability to regenerate, the toxicity is totally reversible. In addition, if further treatment with the drug is necessary, it will often be tolerated at a lower dose. Drug side-effects and secondary effects may also resolve at lower drug dosages. However, since this resolution can occur only at subtherapeutic doses, it may be necessary to start therapy with an alternative agent so that the disease process being treated will be treated optimally.

Drug-drug interactions too are relatively easy to manage. Again, all that is usually required is a dose modification of one or both drugs. However, since undesired drug-drug interactions can often be predicted, in most instances, this type of adverse drug reaction should be stopped before it starts. Before the marketing of any drug, its pharmacodynamic and pharmacokinetic properties are well known and, thus, its ability to potentiate or diminish the actions of any coadministered agent is either known or can be predicted. Physicians can obtain information about potential drug-drug interactions either from reference books⁶ or from the hospital pharmacy's drug information experts.

For type B reactions, especially drug intolerances, the implicated drug may be given again if the previous reaction was mild (eg, tinnitus with aspirin). However, for idiosyncratic reactions, more caution is advised. Adkinson²⁹ suggests that for these reactions, the severity of the reaction must first be considered. If the previous reaction was severe (eg, coumadin-induced skin necrosis in the presence of protein C deficiency), the drug should not be readministered. For previous reactions that were mild to moderate, an unmasked provocation challenge can be done by a specialist familiar with procedures of this type. If no adverse reaction occurs upon rechallenge, the drug can be continued if clinically indicated. If an adverse reaction does occur, both the severity of the reaction and the need for the drug should be assessed before a decision is made about its continuation or discontinuation. Another option is a placebo-controlled masked challenge to ensure that the clinical symptoms shown during the challenge were indeed drug-induced.

If the previous reaction was thought to be hypersensitive in nature, meaning it had immunological features, confirmatory tests should be done if they are available (ie, skin tests for assessment of drug-specific IgE antibodies, or patch tests for assessment of drug-specific T lymphocytes). If a test is available and it is negative, and if the negative-predictive value of the test is known and is high, the patient will not redevelop the hypersensitivity reaction if the drug is readministered. If, however, the negative-predictive value of the test is not known, which is often the case, a negative test cannot be interpreted to mean that the patient is not allergic and, thus, the previous reaction may or may not redevelop if the drug is reintroduced.

If a confirmatory test is not available or if it is available but its negative-predictive value is not known, there are several options. The simplest approach would be to avoid the drug if an alternative drug is available and it is as clinically effective. However, if no alternative exists, a graded challenge with the implicated drug can be considered if the previous reaction was presumed not to be IgE-mediated and if it was not life-threatening. Graded challenges are not indicated in cases where the previous reaction was severe (eg, Stevens-Johnson syndrome or toxic epidermal necrolysis). For these types of reactions, reintroduction of the drug is absolutely contraindicated.

If the previous reaction was presumed to be IgE-mediated, an alternative approach to graded challenge must be taken if the drug is to be readministered. If a skin-test reagent exists, the patient should be skin tested. A positive wheal-and-flare response indicates the presence of drug-specific IgE antibodies (if the proper controls have been done), whereas a negative skin test for tests with a high negative-predictive value (eg, anti-lymphocyte globulin, streptokinase, penicillin) indicates the absence of these antibodies. Since in most instances,

the negative-predictive value is not known, the patient cannot be assumed to lack drug-specific IgE antibodies if the skin test is negative. For these individuals, and for those with positive skin tests, desensitisation—a process by which a drug-allergic individual is converted from a highly sensitive state to a state in which the drug is tolerated—should be done by an experienced allergist if the drug has to be readministered.

Conclusions

The management of patients who present with drug-induced reactions can be frustrating for both the patient and the physician. The patients who are most frightened are those who have had multiple adverse drug reactions. They feel that they are "allergic to everything" and that, if a life-threatening reaction were to develop, they would be doomed. In these instances, physicians should seek the help of a specialist who is familiar with managing drug-allergic patients. Most importantly, both the physician and the patient must be educated. In many cases, non-cross-reacting agents exist and can be used instead. In cases where alternative agents are not available, drug challenge or drug desensitisation may be considered.

All physicians should follow some simple common-sense recommendations when prescribing therapeutic agents to their patients.²⁹ For patients who have multiple antibiotic sensitivities and who seem to need antibiotics frequently, objective evidence of the infection should be obtained before antibiotic treatment is started. If recurrent infections are documented, then they should be treated aggressively to ensure they do not recur. Underlying immunodeficiency as well as any structural abnormalities that may predispose to the development of infections should also be assessed.

Drugs should be given only when they are absolutely indicated. Every drug has an adverse-reaction profile, and some of these reactions are life threatening. Therefore, although adverse drug reactions and drug-induced diseases will continue to exist, the associated morbidity can be reduced if physicians educate themselves about the drugs they prescribe and if judicious prescribing practices are adopted.

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