The adverse effects of drugs

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Adverse drug reactions vary in presentation and severity, and can mimic almost any disease. The article explores the importance of adverse drug reactions in modern clinical practice, highlighting the mechanisms and how to manage patients.

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Drugs prescribed for the treatment of disease themselves cause 'disease' (Pirmohamed et al, 1998). These 'diseases' can be termed drug side-effects or adverse drug reactions (ADRs). This article briefly reviews the current status of ADRs, and provides a synopsis of how a knowledge of mechanisms helps in the clinical management of such patients, together with a brief practical overview on what to expect and what to do when your patient develops an ADR.

WHAT IS AN ADR?

An ADR can be defined as any undesirable effect of a drug beyond its anticipated therapeutic effects occurring during clinical use. The term ADR therefore implies causality, i.e. that the undesirable effects were caused by the drug. This has to be contrasted with an adverse drug event which is an untoward occurrence after exposure to a drug that is not necessarily caused by the drug, i.e. the event may have been caused by the disease process itself or other concomitant treatment.

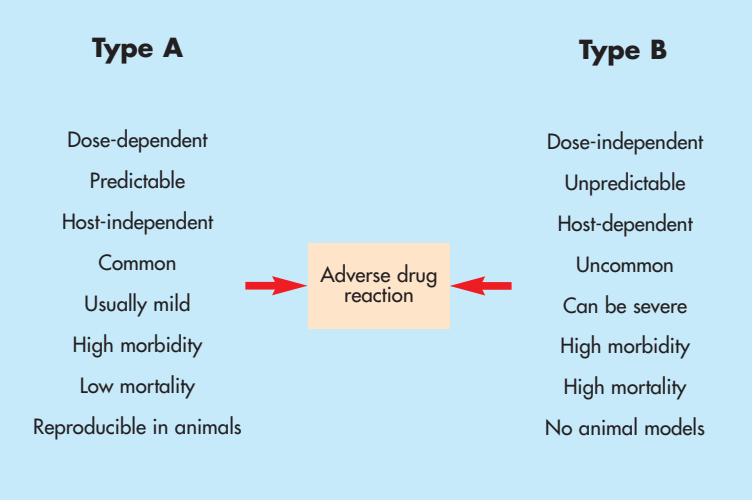

Figure 1. Characteristics of type A and type B adverse drug reactions.

HOW CAN ADRS BE CLASSIFIED?

ADRs can be classified in different ways, but perhaps the simplest from a clinical perspective is where ADRs are divided into two types (*Figure 1*) (Rawlins and Thompson, 1991):

Type A

These are an augmentation of the pharmacology of the drug, and are therefore dose-dependent, and in the majority of cases predictable. These account for approximately 80% of all ADRs.

Type B

These cannot be explained on the basis of the known pharmacology of the drug, and usually do not exhibit a simple relationship between dose and occurrence of toxicity. They are also termed idiosyncratic ADRs: it is important to note that this is a functional term which does not imply any specific mechanism.

HOW COMMON ARE ADRS?

ADRs are a common clinical problem which may account for 2–6% of all hospital admissions (Einarson, 1993; Bates et al, 1995; Classen et al, 1997). A recent meta-analysis in the USA has even suggested that ADRs may be the fourth commonest cause of death after heart disease, cancer and stroke (Lazarou et al, 1998). There are no reliable figures to estimate the burden caused by ADRs in the UK, but it is likely to be similar to that observed in the USA. Therefore, ADRs are likely to represent a major financial burden on the NHS.

HOW DO ADRS OCCUR?

The mechanisms of ADRs are variable and may be complex (Pirmohamed et al, 1998). For the sake of simplicity, the mechanisms of type A and type B ADRs will be described separately.

Type A (pharmacological) ADRs

These may be the result of the primary pharmacology (an exaggeration of the drug's therapeutic actions) or the secondary pharmacology of the drug (an action different from the drug's therapeutic action but still rationalizable from its known pharmacology) (*Figure 2*). The most common mechanism is pharmacokinetic, i.e. concentration of the drug at its site of action is higher than that seen in patients without the ADR. Alternatively, the ADR may be the result of enhanced pharmacological sensitivity.

Patients at the extremes of age are more susceptible to ADRs. Neonates have immature drug metabolizing systems which predisposes them to serious ADRs such as grey baby syndrome with chloramphenicol. In the elderly, around 10.5% of all admissions are the result of ADRs (Williamson and Chopin, 1980). The risk factors are multifactorial; it is known that:

1. Renal and, to a lesser extent, hepatic function alters with age which may reduce drug elimination
2. There is a change in the functioning of pharmacodynamic targets (e.g. receptors, enzymes) with age
3. The elderly have multiple pathologies, some of which are associated with frailty.

All of these contribute to the increased occurrence of ADRs. An additional factor is polypharmacy; it is known that the risk of an ADR increases with the number of drugs prescribed.

Drug–drug interactions are another important source of type A ADRs. Although interactions can affect any aspect of pharmacokinetics (absorption, distribution, metabolism and excretion) or pharmacodynamics, interactions involving drugs which act as inhibitors of the drug metabolizing enzymes have profound safety implications, which have resulted in regulatory action. Examples include terfenadine–erythromycin (which led to QT interval prolongation and torsades de pointes) and mibefradil–simvastatin (which led to rhabdomyolysis).

Type B (idiosyncratic) ADRs

Many different mechanisms for type B ADRs have been described; readers are referred to other publications for a more detailed discussion of the different mechanisms (Park et al, 1992). A large amount of effort has been expended on determining the role of the body's own drug metabolizing system in the pathogenesis of type B ADRs.

Drug metabolism can normally be considered to be a detoxification process, in that it increases the elimination of drugs from the body. However, it can also lead to the formation of unstable and toxic metabolites (a process termed bioactivation) (Pirmohamed et al, 1996). These metabolites, if not detoxified, can bind to essential cellular and circulating proteins, and lead to an ADR, which may be a direct consequence of the effect of the metabolite on cellular and organ function, or it may be indirect, secondary to the initiation of an immune response (*Figure 3*) (Park et al, 1998).

Although toxic metabolites may be formed by any drug which is metabolized, it is important to note that the body is equipped with efficient detoxication mechanisms, which can in effect neutralize the toxic metabolite, and

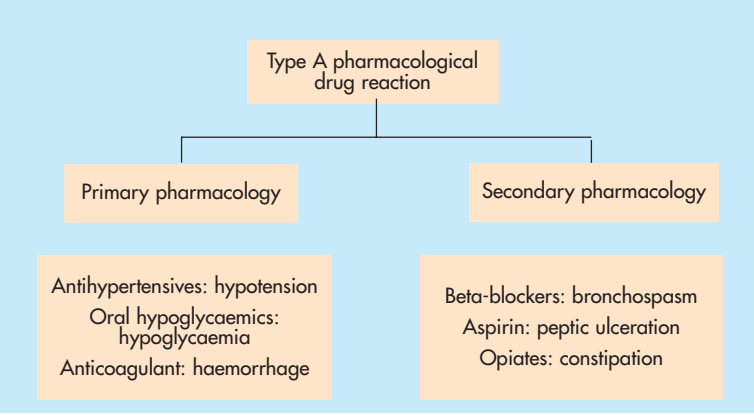

Figure 2. Type A or pharmacological adverse drug reactions can be caused by the primary or secondary pharmacology of the drug.

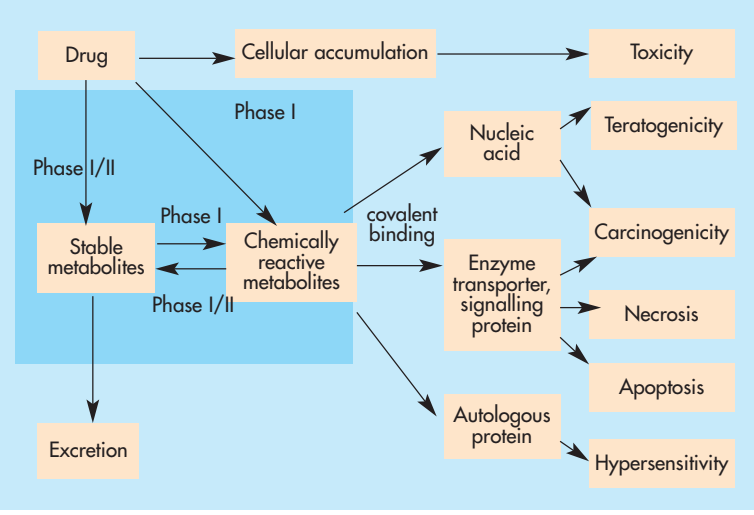

Figure 3. The relationship between drug metabolism and drug toxicity.

allow it to be excreted from the body (a process termed bioinactivation). Thus, it has been postulated that an imbalance between bioactivation and bioinactivation is needed to lead to a type B ADR.

Type B reactions can affect any organ system either individually or in combination (*Table 1*), with the skin, liver and haematological systems among the most common to be affected.

WHAT ARE THE RISK FACTORS FOR ADRS?

Some of the factors predisposing to ADRs have already been mentioned above. Two areas which need further discussion include the role of disease and genetic constitution in predisposition.

TABLE 1.
Examples of organs affected by idiosyncratic toxicity

Organ system	Type of reaction	Drug examples
Generalized reaction	Anaphylaxis	Penicillins
	Hypersensitivity	Temafloxacin
Skin	Toxic epidermal necrolysis	Non-steroidal anti-inflammatory drugs
Liver	Hepatitis	Halothane
Haematological system	Aplastic anaemia	Remoxipride
	Agranulocytosis	Clozapine
	Haemolysis	Nomifensine
Central nervous system	Guillain–Barré syndrome	Zimeldine
Kidney	Interstitial nephritis	Penicillins
Lung	Pneumonitis	Dapsone
Heart	Cardiomyopathy	Tacrolimus
Reproductive toxicity	Etretinate	Various fetal abnormalities

TABLE 2.
Examples of genetic polymorphisms which have been associated with drug toxicity

Genetic polymorphism		Example
N-acetyl transferase	Slow acetylators	Nausea with sulphasalazine
		Peripheral neuropathy with isoniazid
		SLE with procainamide
Debrisoquine hydroxylase (CYP2D6)	Poor metabolizers	Bradycardia with metoprolol
		Hypotension with debrisoquine
		Confusion with nortriptyline
		Hepatotoxicity with perhexilene
Butyrylcholinesterase (pseudocholinesterase) deficiency		Prolonged apnoea with suxamethonium
HLA associations	HLA DR4	SLE with hydralazine
	HLA DR3	Proteinuria with gold
	HLA B38, DR4	Agranulocytosis with clozapine

SLE = systemic lupus erythematosus

Disease

Diseases of the kidney and liver can affect the elimination of hydrophilic and lipophilic drugs respectively, and thus result in type A ADRs. In such cases, the dose of the drug should be reduced or alternative drugs used. Concurrent viral infections can also lead to ADRs, for example, influenza can precipitate theophylline toxicity, and Epstein–Barr virus infection can lead to maculopapular rashes with amoxycillin.

More recently, it has been demonstrated that patients with human immunodeficiency virus (HIV) infection have a higher frequency of hypersensitivity reactions to drugs such as co-trimoxazole (Bayard et al, 1992). Approximately 50% of patients being treated acutely for *Pneumocystis carinii* pneumonia will develop skin rashes, while the rate is about 30% when the drug is being used for prophylaxis. This contrasts with a rate of 3% in HIV-negative patients. The mechanisms of such reactions in HIV-positive patients are unclear, and as such they cannot be predicted and prevented.

Genetic constitution

Defects in genes coding for drug-metabolizing enzymes (Meyer, 1994) and immune response proteins (Lechler, 1994) (which are termed polymorphisms when the rare allele occurs at a frequency of greater than 1%) predispose to both type A and type B ADRs (*Table 2*). Genetic predisposition to type A ADRs is usually the result of a single gene defect, while predisposition to type B ADRs is likely to be the result of defects at multiple gene loci co-existing with environmental factors such as viral infections, akin to polygenic diseases such as diabetes mellitus. Further research is needed in the area to uncover the genetic predisposition in individual patients.

HOW DO ADRS PRESENT CLINICALLY?

Given the fact that ADRs can mimic any disease, it can be difficult to distinguish an ADR from symptoms and signs of the disease the drug is actually being used to treat. This can lead to delays in diagnosis. It is likely that in many cases the correct diagnosis is never made, resulting in an under-estimation of the overall burden of iatrogenic disease. The problem is compounded by the fact that no diagnostic tests are available to diagnose drug-induced disease. The criteria listed in *Table 3* may be helpful in deciding whether a patient has suffered an ADR.

The symptoms exhibited by a patient largely depend on the main organ system affected by

the ADR. Many immune-mediated ADRs, so-called hypersensitivity reactions, are often characterized by a symptom complex which includes fever, rash, arthralgia, lymphadenopathy and eosinophilia (Shear et al, 1988). However, the absence of these manifestations does not exclude the involvement of the immune system in the pathogenesis of an ADR.

HOW SHOULD A PATIENT WHO DEVELOPS AN ADR BE MANAGED?

When a patient develops an ADR, the first decision that needs to made by the clinician is whether to stop the drug. Clearly, if the patient has suffered a serious ADR, then prompt discontinuation of the drug is essential. However, if the side-effect is a type A ADR and is relatively minor, then simply reducing the dose should be sufficient to alleviate symptoms. If dose reduction does not alleviate symptoms, then the drug should be discontinued.

In general, for type B ADRs, the drug needs to be discontinued. However, in some cases, it may be possible to treat through the ADR. This has been practised particularly in HIV-positive patients. For example, mild skin rashes caused by co-trimoxazole often subside despite continuation of the drug. The decision on whether to treat through an ADR depends on the nature and severity of the ADR, and the perceived risk–benefit ratio of continuing therapy.

Most ADRs improve spontaneously when the drug is discontinued although, in some cases, supportive therapy may be required, for example, antihistamines in a patient with a pruritic skin rash. More serious ADRs may require specific therapy. For example, reversal of anticoagulation and blood transfusion may be required in a patient on warfarin who is bleeding. The necessity for, and the type of specific treatment required, clearly needs to be judged on a case-by-case basis.

When a patient suffers an ADR, it is important to report the ADR to the regulatory authorities. This is often forgotten (Belton et al, 1995). Most countries have spontaneous ADR reporting schemes; in the UK, it is termed the yellow card scheme. The ADR reporting schemes are not just data collecting exercises; they often form the basis of drug regulatory action which may range from warnings in the summary of product characteristics (data sheet) to revocation of the product licence (Rawlins, 1995). Such actions are designed to improve drug safety.

In the UK, it is recommended that serious ADRs to established products, and all ADRs to new products (marked by ▼ in the British National Formulary) should be reported on yellow cards. A common misapprehension is that only those reactions where one has proof that the drug is responsible should be reported. As has been pointed out, one cannot always be certain of the causal association because of confounding factors, and therefore, if an ADR is suspected, and if it fits in with the reporting criteria, then it should be reported. Indeed, if you are in doubt as to whether to report the ADR, it is safer to report it anyway.

CAN ADRS BE PREVENTED?

Theoretically, it should be possible to predict and prevent all type A ADRs. More skillful prescribing, by being aware not only of the pharmacology of the drug, but also of other drugs being taken by the patient, and their diseases, can go some way to achieving this goal.

Many type B reactions occur in patients who are prescribed the same drug, or a very similar

TABLE 3.
Steps to determine whether a drug is responsible for an adverse effect

What is the timing between the start of drug therapy and the reaction?	Most reactions occur soon after commencing drug therapy, although some may be delayed for months or even years
Does the reaction improve when the drug is withdrawn or dose reduced?	Most reactions improve on drug withdrawal and type A reactions can also improve if the dose is reduced
What happens when the patient is rechallenged with the drug?	Recurrence on rechallenge provides good evidence that the drug is responsible for the adverse effect. However, this is rarely possible, particularly for serious reactions, because of the danger to the patient
Have concomitant drugs and other non-drug causes been excluded?	An adverse drug reaction is a diagnosis of exclusion since there are no specific laboratory tests available. It is important to exclude non-drug causes clinically as well as by performing relevant investigations
Has the reaction been reported before?	If the reaction is well recognized, it may be mentioned in the British National Formulary, Monthly Index of Medical Specialities or the Summary of Product Characteristics, or may have been reported in the literature

agent to which they have had a previous adverse reaction. For this reason, the GP and hospital medical records and inpatient prescription sheets should all be clearly marked, so that the prescriber is aware of previous serious ADRs. Additionally, with some drugs it may be possible to prevent type B ADRs or at least to reduce the severity of the reaction. For example, monitoring of the patient with simple laboratory tests such as the white cell count in the case of agranulocytosis or serum transaminases with hepatic injury may allow the subclinical detection of toxicity, followed by withdrawal of the drug before the patient develops any clinical symptoms.

There are many drugs used clinically where it is recommended that patients have regular laboratory monitoring, e.g. patients on clozapine require weekly full blood counts because of the risk of agranulocytosis (Pirmohamed and Park, 1997).

CONCLUSIONS

ADRs are common, and represent an unnecessary economic and clinical burden on already over-stretched NHS resources. A knowledge of the drug, the patient and their disease, which would aid more skillful prescribing can help in preventing the more common type A (pharmacological) ADRs, while an understanding of the mechanisms of type B (idiosyncratic) reactions will help in devising preventative strategies for these ADRs.

Increased emphasis on ADRs in new medical curricula as well as part of continuing medical education would also help in highlighting the importance of ADRs, ultimately allowing a reduction in the burden posed by what can on many occasions be a potentially fatal complication of drug therapy. HM

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KEY POINTS

- Adverse drug reactions are common.
- They can be divided into two basic types: type A (pharmacological) and type B (idiosyncratic).
- Diagnosis is usually made on clinical grounds based on the temporal relationship between the start and finish of drug treatment.
- Discontinuation of drug therapy, or in some cases, reduction of dose, is usually all that is needed to allow resolution of the adverse reaction.
- Reporting on yellow cards should always be considered when a patient develops a clinical manifestation which is suspected to be an adverse drug reaction.