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ADVERSE DRUG REACTIONS

SUMMARY

-  An adverse drug reaction (ADR) is a response to a drug that is noxious and unintended and occurs at doses normally used in man.
-  ADRs are a leading cause of morbidity and mortality in the western world.
-  Most ADRs are dose dependent, predictable and may be avoidable.
-  Drug groups which most often contribute to ADRs are NSAIDs, psychotropic drugs and cardiovascular drugs.
-  Age, female gender and the number of drugs taken concomitantly are the most important risk factors for ADRs.
-  ADR reporting is vital for drug safety.

INTRODUCTION

An adverse drug reaction (ADR) as defined by the World Health Organisation (WHO) is 'a response to a drug that is noxious and unintended and occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for the restoration, correction or modification of physiological function'.¹ An ADR can be distinguished from an adverse drug event in that the latter is an adverse outcome that occurs while a patient is taking a drug, but is not necessarily attributable to it.¹ The terms adverse reaction and adverse effect are often used interchangeably, but it is the *drug* that has an *adverse effect* whereas it is the *patient* that experiences an *adverse reaction*.

An estimated 100,000 deaths occur per year due to ADRs, making it a leading cause of death in the U.S.² It has been estimated that 30% of hospitalised patients suffer one or more ADR, 3% of these have an ADR of considerable severity and 0.3% may die as a consequence. Up to 5% of hospital out-patients may require hospitalisation to prevent or manage ADRs.³ A large proportion of adverse effects probably occur in the community and never lead to hospital admission.^{4,5} It is estimated that about half the cases of drug related injury are from potentially avoidable ADRs.¹

CLASSIFICATION OF ADRs

Type A reactions

Approximately 80% of ADRs are type A, i.e. are dose dependent and predictable, based on the pharmacology of the drug.⁶ The pharmacology can be further defined as either primary or secondary, for example bleeding with anticoagulants is an extension of their primary pharmacology, whereas dry mouth is an effect of the secondary pharmacology of tricyclic antidepressants, i.e. their antimuscarinic action.

Type B reactions

In contrast idiosyncratic (type B) reactions are bizarre and cannot be predicted from the known pharmacology of the drug.^{6,7} Idiosyncratic reactions include IgE mediated reactions such as anaphylaxis, teratogenicity and carcinogenicity, in addition to reactive metabolite syndromes, e.g. hypersensitivity syndrome reactions, serum sickness-like reactions, and drug induced lupus.⁶ In general such reactions are more common in those with a history of allergy, such as asthmatics.

The distinction between type A and type B is everchanging, as pharmacogenetics progresses, with more reactions being classified as pharmacological rather than idiosyncratic.⁸ Pharmacogenetics/pharmacogenomics is the study of how an individual's genetic inheritance affects the body's response to drugs.⁹

More recently, additional types of ADRs have been suggested, such as chronic (type C) and delayed (type D) effects, as well as withdrawal or end of use syndromes (type E) and therapeutic failures (type F).¹⁰

RISK FACTORS FOR ADRs

Almost all studies revealed extremes of age and the number of drugs taken concomitantly as the most important risk factors for an ADR.¹⁰

Most ADRs are dose-dependent and are probably preventable.¹¹ No particular drug or drug class appears to cause serious morbidity disproportionate to the level of use. Intuitively drugs with a low therapeutic ratio require consideration, as with these drugs the margin between the therapeutic and toxic doses is small.(Table 1) The only consistently independent predictor of ADRs is the absolute number of concurrent medications being taken.¹¹ It is therefore important to review medication at every opportunity.¹²

Drugs which most often contribute to ADRs are also those most often used in clinical practice, and include NSAIDs, psychotropic drugs and cardiovascular drugs, e.g. diuretics and digoxin.¹¹ One report proposed that deaths from the toxicity of NSAIDs could be the 15th most common cause of mortality in the United States.¹³ Pregnancy, lactation, childhood, being elderly, decreased renal clearance or haemodialysis all have characteristic features which may allow medicines to exhibit effects that would otherwise be rare or would not occur.¹⁵ In neonates, a major predisposing factor may be the immaturity of the enzyme systems responsible for the metabolism of drugs, which can lead to the decreased clearance of many drugs.²

A 'prescribing cascade' may explain part of the problem of ADRs in old age. The cascade of events begins when an ADR is misinterpreted as a new medical condition. A new drug is then prescribed and the patient is at risk of developing more adverse effects relating to this unnecessary treatment. Recognition of this sequence may be useful in avoidance of ADRs.¹⁶

Interestingly, female gender has also been identified as an important risk factor, reasons proposed for this are the greater degree of polypharmacy, the increased bioavailability of drugs and the greater sensitivity of their target organs.^{10,17}

It is worth remembering that even with appropriate drug use, ADRs to medications will still occur.¹⁴

Table 1: Examples of drugs with a narrow therapeutic index

Antiarrhythmics e.g. amiodarone, flecainide and quinidine	Cytotoxics/immunosuppressants e.g. ciclosporin, azathioprine
Anticonvulsants e.g. phenytoin	Lithium
Cardiac glycosides e.g. digoxin	Theophylline
Aminoglycosides e.g. gentamicin	Oral anticoagulants e.g. warfarin

DETECTING/ DIAGNOSING ADRs

If a patient is taking medicines, and presents with an illness, the differential diagnosis should include the possibility of an ADR.¹⁶ The first step is to find out whether a patient is taking a medicinal product, including: OTC preparations, products that may not be thought of as medicines (such as herbal or traditional remedies, recreational drugs, or drugs of abuse) and long term treatments that the patient may forget,¹ e.g. oral contraceptives, HRT and topical preparations. It is then necessary to determine whether the illness could be due to the drug.⁶ Most naturally occurring diseases may be mimicked by drug reactions and accurate diagnosis depends on the degree of clinical alertness.(Table 2)

There is some evidence that in the future the use of pharmacogenomics could help to reduce ADRs, e.g. arrhythmias with thioridazine, as it aims to predict which patients are likely to respond to a particular drug and which patients are likely to have significant ADRs.^{12,18} Clinical trials, case reports, spontaneous reporting systems, and formal epidemiological studies can all detect ADRs.⁶

Table 2: Criteria for diagnosing ADRs

- Nature of reaction (the pattern of the ADR may fit the known pharmacology of the drug)
- Temporal relationship with drug exposure (i.e the time between the use of the drug and the occurrence of the reaction)
- History of similar reactions (patient may previously have had a similar reaction to a different drug in the same class)
- Investigations e.g. laboratory tests
- Dechallenge (effect of dose reduction or drug withdrawal)
- Rechallenge (may not be possible for ethical reasons)

MANAGEMENT OF ADRs

Rapid action is important if the ADR is of a serious nature, e.g. anaphylactic shock.¹ In less serious cases the decision to stop the drug is probably based on the prescriber's assessment of the risks and benefits of continuing treatment, and the patient's wishes.¹²

If several medicines could be causative, the drugs least likely to result in harm if withdrawn should be withdrawn first, preferably one at a time, depending on the severity of the reaction. If the reaction is likely to be dose-related, dose reduction should be considered. If a patient cannot manage without a drug that has caused the adverse reaction, providing symptomatic relief while continuing the essential treatment is a consideration.¹ In general practice ADRs are often mild and self-limiting, but a problem arises if the patient is labelled as having an allergy to a drug, e.g. penicillin when it is not entirely certain if this is the case, and therefore the patient is denied this drug or group of drugs in the future.¹²

REPORTING ADRs

It was the thalidomide disaster which led to the setting up of a formal ADR reporting system.⁶ The collection of ADR reports is vital to ensure continued effective surveillance of the safety of licensed medications.¹⁹ Reporting an ADR depends on the reporter suspecting a reaction, and having the confidence and time to commit the suspicion to paper.²⁰ Relatively few patients are exposed to a drug by the time it is released onto the market.⁶ Although fraught with certain limitations such as underreporting, the use of postmarketing surveillance is still very critical in collecting data on drug safety because the true adverse reaction profile of a drug is often not revealed until it has been widely used. This is especially true for the idiosyncratic ADRs that are difficult to predict. Approximately 2-3 years of postmarketing experience is required to fully understand the safety profile of a new drug.² However problems can also emerge after an agent has been used 'safely' for many years, e.g. terfenadine, until its effects on the QT interval were discovered.⁶

Approximately half of all drug withdrawals occur within 2 years of introduction of the drug.²¹ It has been suggested that clinicians should avoid using new drugs if older, similarly efficacious agents are available, until a better understanding of their safety profile is obtained.²¹ There are many type A effects that take months or even years to develop, e.g. carcinogenicity. For this reason serious reactions to established products should also be reported.¹⁵

The Irish Medicines Board (IMB) is responsible for the national reporting system of monitoring ADRs. It is not necessary to determine a causal relationship between a drug and subsequent event, prior to reporting a suspected ADR (Table 3). Doctors, dentists, pharmacists and nurses are requested to report to the IMB through the 'Yellow Card system'. Pharmaceutical companies are obliged to report ADRs, as a condition of their authorisation (i.e. licence) to market products. Reports received from healthcare professionals and companies are entered onto the IMB's database, which currently includes approximately 30,000 reports.

National regulatory authorities send anonymous details of ADR reports to the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden for inclusion on their database. This global information is available to all countries participating in the programme, and is analysed by the Collaborating Centre and their panel of expert reviewers.¹

Interestingly, unexpected therapeutic ineffectiveness is an important event, which may be associated with issues relating to product quality and should be reported whether it is a true adverse reaction or not.²²

A problem with spontaneous reporting is that less than 10% of all serious, and only 2-4% of non-serious adverse reactions are reported. From a total of 23 million General Medical Services (GMS) prescriptions in the year 2000, the IMB received 1,407 suspected ADR reports.^{23,19} All healthcare professionals need to be aware that ADR reporting is part of overall patient care, and is not simply an afterthought.⁷ Recently there has been a large rise in ADR reports in the developed world and this may be attributable to both better safety reporting and the relatively fast launch of new drugs in developed markets.²⁴

Table 3: The following should be reported to the IMB

- All suspected reactions to new products (on the market less than 2 years)
- *Serious* suspected reactions to established products.*
- Any suspected increase in the frequency of non-serious reactions.
- All suspected reactions to vaccines.
- All suspected teratogenic effects.

* *Serious* reaction is defined as one which is fatal, life threatening, results in persistent or significant disability/incapacity, results in or prolongs hospitalisation. This definition also includes congenital abnormalities or birth defects and serious adverse clinical consequences.¹⁹

SOURCES OF INFORMATION ON ADRs

- Summary of Product Characteristics/ Data Sheet Compendium
- British National Formulary (BNF)
- Martindale - The Complete Drug Reference
- Meyler's Side Effects of Drugs
- National Medicines Information Centre (NMIC)
- Irish Medicines Board (IMB)
- Pharmaceutical companies

CONCLUSION

The importance of ADRs is often underestimated, they are common and can be life threatening and unnecessarily expensive. Each healthcare professional shares a responsibility for identifying risk factors for ADRs, and using that knowledge to reduce their occurrence. The old and the very young and those on multiple medications are at the highest risk of developing an ADR. Even with appropriate drug use ADRs to medication will still occur. It is estimated that about half the cases of drug-related injury are from potentially avoidable ADRs, so there is much room for improvement. It is good practice to review medication at every opportunity. In future with a knowledge of genetics it will be possible to predict susceptibility to an increasing number of drug-induced diseases. At present pharmacovigilance is predominantly based on spontaneous reporting and is primarily helpful in detecting type B effects and unusual type A effects. Efforts to improve the reporting of ADRs by healthcare professionals will increase the detection of such reactions.

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