Anticipating, investigating and managing the adverse effects of drugs

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Adverse drug reactions (ADRs) are common. A prospective analysis of 18,820 patients showed that 6.5% of admissions were due to ADRs, the affected patients being hospitalised for a median of eight days and accounting for 4% of the hospital bed capacity at an annual cost to the NHS of nearly £0.5 billion per annum.[1] ADRs can also occur after hospital admission. There are no recent data on the prevalence, although studies pre-1990s suggest that the figure may be greater than 10%. ADRs also cause death; they were estimated to be the fourth to sixth leading cause of death in the US in 1994.[2] It is therefore likely that physicians will encounter patients with ADRs in their daily practice. The key to appropriate management is prompt recognition that the patient's new symptoms and signs may be drug-related – indeed, this may be life-saving.

Clinical assessment of the patient

Any bodily system can be affected by ADRs and any disease process mimicked.[3] ADRs have taken over as the mimic of disease from syphilis and tuberculosis. The clinical picture is further complicated because the same drug can produce diverse manifestations in different patients and the severity of the reactions also varies widely.

Drug history

The history is by far the most important part of any clinical assessment.[4] A good drug history is essential. It is important to ask not only about prescription drugs (verified, if possible, by the relatives and/or general practitioner) but also about illicit drugs and herbal and homeopathic medicines. The use of complementary/alternative medicines is widespread, and about one in five people will have purchased over-the-counter herbal or homeopathic remedies in the previous year,[5] while one in three patients undergoing surgery admits to using herbal medicines,[6] often without having informed their own doctor. Herbal remedies can themselves cause ADRs (eg kava kava and hepatotoxicity) or interact with prescribed medicines (eg St John's wort).

Symptoms and signs

The symptoms and signs exhibited by a patient largely depend on the main organ system(s) affected by the ADR. It is important to focus the clinical assessment on that system and critically ascertain whether the signs and symptoms are in keeping with a drug-related problem or are due to non-drug induced disease. To this end, knowledge of the adverse effect profiles of the different medicines the patient may be taking is important. This can be obtained from reference textbooks[7] and/or drug information centres which will be able to carry out literature searches and query the most recent product information literature. On occasion, this may lead to unexpected conclusions (Box 1). Inevitably, many patients now tend to be on multiple drugs. In such cases, deciding which drug is responsible can be difficult, although following a few simple rules (remembered by the mnemonic TREND) may help in the identification of the culprit drug (Table 1).[4]

In some cases, the signs of the ADR may be more general. For example, drug hypersensitivity reactions are often characterised by a symptom complex that includes fever, rash, arthralgia,

BOX 1. A CASE HISTORY

A 37-year-old woman with rheumatoid arthritis was admitted with a seven-day history of fever, abdominal pains, bloody diarrhoea and eosinophilia. There was no history of travel abroad and no family members had similar symptoms. She had been on diclofenac for 12 months and had started gold three months prior to admission. Stool cultures were negative and sigmoidoscopy revealed an inflamed bowel with small areas of ulceration. An initial diagnosis of ulcerative colitis was made; she was started on steroids but failed to improve. A literature search revealed that gold is a cause of colitis. Withdrawal of gold and continuation of steroids led to complete resolution of symptoms. The steroids were gradually withdrawn; two years later, the patient remains free of symptoms of colitis.

Key Points

- **Adverse drug reactions (ADRs) are common, causing and prolonging hospitalisation**
- **The clinical manifestations of ADRs are protean and can mimic any disease**
- **The key to appropriate management of ADRs is prompt detection**
- **Diagnosis of an ADR is by exclusion of other diseases and a simple causality assessment**
- **Management may include dose reduction and/or withdrawal depending on the nature and severity of the reaction, accompanied if necessary by specific therapies**

KEY WORDS: adverse drug reaction, causality, hypersensitivity, pharmacogenetics

lymphadenopathy and eosinophilia; they can be caused by a wide range of drugs including antibiotics, anticonvulsants, non-steroidal anti-inflammatory drugs (NSAIDs), antiretrovirals and allopurinol. Concurrent viral infections also increase the risk of allergic drug reactions.[8] Thus, patients with HIV are more likely to develop hypersensitivity to antimicrobials such as co-trimoxazole (used for the treatment of pneumocystis pneumonia), while infectious mononucleosis increases the risk of rash in patients given amoxicillin by a factor of 58.[9]

Drug allergy

Assessment of the past medical history is also important as this may allow anticipation of ADRs. It is always important to ask about drug allergies. However, many patients claim to be allergic to a drug, but close questioning reveals that they are merely intolerant. For example, many patients who claim to be penicillin allergic have actually had vomiting or diarrhoea.

Cross-reactivity

A good history of drug allergy raises the possibility that the patient may be cross-reactive to other structurally similar drugs. This is perhaps most important with the beta-lactam antibiotics, where cross-reactivity rates as high as 20% have been quoted for penicillins and cephalosporins. However, a recent analysis showed that the rates of cross-reactivity may be lower. The frequency of cross-reactivity with cephalosporins in patients with a known history of immunoglobulin (Ig) E mediated hypersensitivity to penicillin in the presence of a positive skin test for penicillin allergy was 4.4%, falling to 0.6% when the skin test was negative.[10] This suggests that cephalosporins should be avoided in patients with positive skin results with penicillin.

Other factors

Any factors that predispose to the development of ADRs should also be elicited in the history. For example, patients with atopy and autoimmune disease are at an increased risk of developing immediate and delayed type hypersensitivity reactions, respectively. Anticipating drug–drug interactions is also important in avoiding ADRs – up to one in six ADR-related admissions may be due to interactions.[1]

Table 1. Steps to determine whether a drug is responsible for an adverse reaction (TREND).

Temporal relationship	*What is the timing between the start of drug therapy and the reaction?* Most reactions occur soon after commencing drug therapy; anaphylactic reactions can occur within hours, while hypersensitivity reactions typically take 2–6 weeks. Other reactions such as bone density changes may be delayed for years.
Rechallenge	*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, rechallenge is rarely possible, particularly for serious reactions, because of the danger to the patient. More rapid occurrence following re-exposure to the drug than on secondary exposure indicates an immune-mediated pathogenesis.
Exclusion	*Have concomitant drugs and other non-drug causes been excluded?* An adverse drug reaction is a diagnosis of exclusion since no specific laboratory tests are available. It is important to exclude non-drug causes both clinically and by performing relevant investigations.
Novelty	*Has the reaction been reported before?* If the reaction is well recognised, it may be mentioned in the manufacturer's literature or have been reported in the medical literature. An opportunity should always be taken to search reference databases such as Medline systematically; this can provide valuable insight into the appropriate management of patients with what may be a relatively rare reaction. Drug information centres can also provide useful information.
Dechallenge	*Does the reaction improve when the drug is withdrawn or the dose reduced?* Most, but not all, reactions improve on drug withdrawal although the recovery phase can be prolonged. In rare instances, an autoimmune phenomenon may be set up and thus the reaction will not improve on drug withdrawal.

Investigation of patients with adverse drug reactions

An ADR is a diagnosis of exclusion since no specific laboratory tests are available. It is therefore important to exclude non-drug causes clinically as well as by performing relevant investigations. Patients with severe ADRs should have routine tests, such as full blood count, liver and renal function, to identify any subclinical involvement of other organs. For example, in patients with suspected drug allergy, there may be an increase in C-reactive protein, eosinophilia and abnormal liver function tests. The investigations to be performed in a patient with a suspected ADR should reflect the nature of the reaction. For example, a patient with NSAID-induced gastrointestinal (GI) bleeding should have haematological evaluation, endoscopy to assess the nature of the GI injury and assessment of *Helicobacter pylori* status.

For allergic ADRs, various tests such as the lymphocyte transformation test and basophil degranulation assay have been developed, but these are not sensitive and specific enough for routine diagnostic use. A useful serum marker for assessing mast cell activation is beta-tryptase – levels greater than 5 μg/l are seen in systemic anaphylaxis if taken within 1–2 hours of the episode.[11] Skin testing can be performed for IgE-mediated reactions to drugs such as penicillin.[12] The test has a high negative predictive value

since more than 98% of patients with a history of penicillin allergy but who are skin-test negative can safely receive the antibiotic (with respect to the risk of anaphylaxis).

Management of patients with adverse drug reactions

When a patient develops an ADR, the first decision that the clinician needs to make is whether to stop the drug. If the patient has had a mild type A ADR, simply reducing the dose should be sufficient to alleviate symptoms. If dose reduction does not alleviate symptoms, the drug should be discontinued. Clearly, if the patient has suffered a serious ADR, prompt discontinuation is essential. In general, for type B ADR, the drug needs to be discontinued – indeed, prompt discontinuation for some ADRs such as anticonvulsant-induced skin reactions prevents progression to more serious reactions and reduces mortality.[13]

Most ADRs improve spontaneously when the drug is discontinued, although supportive therapy may be required in some cases, 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 needs to be judged on a case-by-case basis.

Desensitisation

Desensitisation is carried out on occasion for patients with allergic reactions to certain drugs, for example, co-trimoxazole in HIV-positive patients.[14] This may also be necessary in certain patient groups, for example patients with cystic fibrosis, who have a need for repeated courses of antibiotics but have a high frequency of antibiotic allergy. It is important to note however that desensitisation is not without risk and can result in fatalities; it should be performed only by specialists in settings with adequate resuscitation facilities.

Reporting of adverse drug reactions

When a patient suffers an ADR, it is important to report it to the Medicines Healthcare Products Regulatory Agency in the UK on a yellow card as per reporting criteria. This voluntary system (now 40 years old) has had many successes in identifying new ADRs that have subsequently led to regulatory action. However, it suffers with the problem of under-reporting, with only 10% of serious ADRs being reported. Reporting has now been opened up to other professions, including pharmacists and nurses, and is due to be piloted soon in patients. It is important to remember that the yellow card system is there to identify new signals of ADRs – that is, it generates hypotheses which then have to be confirmed using other methodologies.

Predicting adverse drug reactions

Individual predisposition to an ADR is, at least partly, genetically determined.[15] The completion of the human genome project and development of the SNP map, and soon the haplotype map, will provide us with an unprecedented opportunity to determine the degree to which variability in response is genetically determined and whether pre-prescription genotyping in a clinical setting leads to avoidance of the ADR in a cost-effective manner. Many ADRs that have a genetic basis have been identified (Table 2), but only the assessment of the thiopurine methyl transferase polymorphism has had a major clinical impact.

Table 2. Some genetic factors known to predispose to adverse drug reactions

Drug	Adverse effect	Gene defect
Abacavir	Hypersensitivity reaction	HLA B*5701
General anaesthetics	Malignant hyperthermia	Ryanodine receptor
Isoniazid	Peripheral neuropathy	N-acetyl transferase type 2
6-Mercaptopurine	Bone marrow suppression	Thiopurine methyl transferase
Oral contraceptives	Venous thromboembolism	Factor V Leiden
Primaquine	Red cell haemolysis	Glucose-6-phosphate dehydrogenase
Suxamethonium	Prolonged apnoea	Butyryl cholinesterase

Conflicts of interest

None.

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Rational prescribing: the principles of drug selection and assessment of efficacy

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Most experienced prescribers believe that the principles of rational prescribing underpin their choice of therapy. However, without a robust understanding of the basis for decisions, drug choice can become formulaic and ignore individual patient variability. Rational prescribing should:

- maximise effectiveness
- minimise risks
- respect patient choice, and
- minimise costs.

A logical sequence of events usually precedes a rational prescription, comprising:

- making a diagnosis (or differential diagnoses)
- determining the prognosis of the condition to be treated
- determining the goal(s) of treatment (eg curative, symptom-relieving, preventive or, occasionally, an aid to the diagnostic process), and
- selecting an appropriate type of treatment.

It is unusual for only one treatment option to be available and a selection is made from a range of possible approaches. For example, an explanation may be sufficient to satisfy a patient with brief, infrequent episodes of supraventricular tachycardia. For longer episodes, vagotonic manoeuvres may terminate the symptoms. More frequent or symptomatic tachycardias may be suppressed by a beta-blocker or calcium channel antagonist, and it may also be appropriate to consider an electrophysiological study with a view to ablation of the originating focus.

Evidence from large-scale randomised controlled trials (RCTs) is often used to guide the choice of treatment. However, many assumptions are made when extrapolating evidence from a highly selected population sample to general clinical practice, ignoring exclusion criteria that were applied during recruitment. A drug that is superior in clinical trials may prove less effective in clinical practice because of variability in individual responses or be less suitable for an individual because of potential adverse effects. In the former situation, there is no reliable way to determine the probability of a successful outcome in an individual; in the latter, good clinical judgement should override the results of clinical trials.

Assessing treatment outcomes

When a drug is chosen as part of the therapeutic strategy, it is important to monitor the outcome of that choice. Measuring the desired therapeutic effect may seem intuitive, but is often elusive. The ideal end-point will be a relevant clinical outcome, determined by an objective measure, such as survival after antibiotic treatment for meningococcal septicaemia, control of ventricular rate in atrial fibrillation or the frequency of symptoms in angina. Often, the end-point will be subjective, such as relief of pain in arthritis or the ability to perform activities of daily living in Parkinson's disease. In clinical trials, such subjective outcomes will be measured with a validated tool such as a visual analogue scale or a quality-of-life questionnaire. In clinical practice, patient satisfaction with the prescribed treatment will be the usual criterion of success.

Surrogate end-points

Surrogate end-points can be a valid and useful outcome measure if the effect of an intervention on the surrogate end-point fully predicts the effect on the desired clinical outcome. However, they