Adverse Drug Reactions and Interactions: Mechanisms, Risk Factors, Detection, Management and Prevention

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Introduction

Adverse drug reactions (ADRs), of which adverse interactions are a special case, are a major cause of morbidity in the community. They are also reported to account for up to 5 per cent of all medical admissions to hospital (Grahame-Smith and Aronson, 1992; Aronson and White, 1996) and they are occasionally fatal. In the USA, it has been suggested that they are between the fourth and sixth commonest cause of death in hospitalized patients (after heart disease, cancer and stroke and around the same frequency as pulmonary disease and road-traffic accidents) (Lazarou et al., 1998).

ADRs are often difficult to differentiate from non-drug-related disease. Many factors, such as concomitant treatment and disease, can cloud their identification, and there are few specific laboratory or clinical methods to confirm them. In clinical practice it is thus often difficult to separate adverse events from adverse reactions, particularly in the case of previously unrecognized reactions. Most doctors often rely on their own experience or the experience of others of similar problems before accepting that a drug might have caused the event. For these reasons, ADRs remain an important clinical and public health problem, although many ADRs are predictable and, therefore, potentially avoidable from the known pharmacology of the drug and the characteristics of the patient.

Classification of adverse drug reactions

ADRs can occur in two forms: commonly they are ‘type A’ or ‘dose-related’ adverse reactions, which are an ‘accentuation’ of normal drug effect (Rawlins and Thompson, 1977). Thus, digoxin slows the heart rate in a dose-dependent fashion, but this may become an adverse effect if the heart rate becomes too slow. Type A reactions make up perhaps 75
per cent of all adverse reactions, but they are proportionately less likely to have fatal consequences than type B reactions (Table 2.1). Nevertheless, because their onset is often gradual, they may remain unrecognized for some time and produce considerable morbidity to the patient.

<table>
<thead>
<tr>
<th>Table 2.1</th>
<th>A classification of adverse reactions, revised from Rawlins and Thompson (1977)</th>
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<tbody>
<tr>
<td></td>
<td>Type A (accentuated)</td>
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<tr>
<td>Dose relationship</td>
<td>Yes</td>
</tr>
<tr>
<td>Frequency</td>
<td>Common</td>
</tr>
<tr>
<td>Mortality</td>
<td>Low</td>
</tr>
<tr>
<td>Morbidity</td>
<td>High</td>
</tr>
<tr>
<td>Treatment</td>
<td>Stop drug or reduce dose</td>
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Type B reactions are unpredictable and often ‘bizarre’ reactions to a drug, which may be present at an extremely low concentration. These reactions tend to be sudden and often dramatic in onset and are usually quickly recognized, although some, particularly those involving anaphylaxis, may be fatal.

Grahame-Smith and Aronson (1992) have extended the original Rawlins and Thompson classification described above to include type C ADRs and type D reactions. Type C (chronic) reactions are long-term drug effects including adaptive changes (e.g. drug tolerance) and withdrawal (rebound) effects. Type D (delayed) reactions involve carcinogenesis and effects associated with reproduction. Although this classification highlights ADRs that may have been given inadequate consideration in the past, it relies on both temporal and mechanistic features. In this chapter, these issues will be addressed within the context of the original classification.

**Risk factors for type A adverse reactions**

Type A reactions, being an extension of the normal pharmacological effect of the drug, occur when the concentration of the drug at the site(s) of action is increased above the normal therapeutic level (Table 2.2). This may occur when the dose administered is excessive for that individual either because:

- elimination mechanisms are compromised (pharmacokinetic causes), or

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<tr>
<th>Table 2.2</th>
<th>Risk factors for type A ADRs</th>
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<tr>
<td>Pharmacokinetic</td>
<td>Pharmacodynamic</td>
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<tr>
<td>Renal disease</td>
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<tr>
<td>Liver disease</td>
<td>Liver disease</td>
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<tr>
<td>Cardiac failure</td>
<td>Cardiac failure</td>
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<tr>
<td>Extremes of age</td>
<td>Extremes of age</td>
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<tr>
<td>Pharmacogenetic</td>
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</table>
• the target organ is excessively sensitive to a given drug concentration (pharmacodynamic causes)

Both of these mechanisms tend to go hand in hand and are seen at the extremes of life, as well as in patients with renal or liver disease. Other individuals may be at increased risk because of genetically inherited factors, and these will also be described.

Pharmacological and pharmaceutical factors

Certain drugs are associated with an increased risk of adverse reactions or interactions. These tend to be agents with a low therapeutic ratio (i.e. the difference between a therapeutic and toxic dose is low) and include oral anticoagulants, oral hypoglycaemic agents, some antihypertensives, many cytotoxic agents, corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs) and digoxin. In addition to these pharmacological factors, the pharmaceutical formulation may predispose to ADRs. Changes in formulation have, in the past, been associated with increased bioavailability of certain drugs with a low therapeutic ratio (e.g. phenytoin and digoxin) and subsequent type A toxicity. The likelihood of this problem is now low because of the strict bioequivalence criteria insisted upon by national licensing bodies. Nevertheless, the formulation may cause local toxicity, e.g. the intestinal perforation seen in association with a certain form of indomethacin in the early 1980s (Day, 1983) or the colonic strictures reported in association with high-dose pancreatic enzyme supplements (Fitzsimmons et al., 1997). It is also rare now for the fillers, binders, surfactants, dyes or other excipients, which constitute around 90 per cent of the mass of many formulations, to cause type A toxicity. However, serious problems have occurred, such as fatal renal failure in Bangladeshi children caused by diethylene glycol in paracetamol elixir (Hanif et al., 1995).

Pharmacokinetic risk factors

These include several situations when elimination mechanisms are impaired. These include reduction in renal excretion of drugs, as well as impaired drug metabolism, largely due to liver disease (Routledge, 2002).

Renal disease

Most drugs are lipid soluble and, therefore, are first metabolized to more polar (water-soluble) compounds before the metabolites can be excreted in the urine. Several clinically important compounds (e.g. digoxin, aminoglycoside antibiotics, lithium, captopril and potassium-sparing diuretics) are already relatively water soluble and are not markedly bound to plasma proteins and so undergo glomerular filtration. In other cases, the active metabolite of an inactive drug (prodrug) may be excreted largely unchanged by the kidney – examples include oxypurinol, the active metabolite of allopurinol, and enalaprilat, which is the active metabolite of enalapril. In renal failure, glomerular filtration rate (GFR) declines progressively and is a useful marker of renal dysfunction. Normally, the GFR in an adult is around 120 ml/mm and the clearance of drugs exclusively by this process cannot exceed this value. Mild renal failure is defined by a GFR of 20–50 ml/min, moderate renal failure by a GFR of 10–20 ml/min and severe renal impairment by a GFR of less than 10 ml/mm. Drugs for
which glomerular filtration is an important pathway may accumulate in renal failure unless the dose is reduced accordingly.

Active tubular secretion is the other important excretory process in the kidney. Weak electrolytes (acids and bases) are secreted into the proximal tubular fluid and digoxin may be secreted by the distal tubule. This is an energy-dependent process and drugs can be effectively cleared, with a tubular secretion of ampicillin of around 400 ml/min in subjects with normal renal function. Tubular secretion is relatively spared in renal impairment, so dose reduction of those drugs for which this process contributes significantly to total clearance may not be necessary unless renal impairment is severe.

**Liver disease**

The liver is the largest metabolic organ and quantitatively the most important, although the skin, gut, lungs, kidney and white cells have some limited metabolic capacity. Many drugs are lipid soluble, and even if a substantial proportion was not protein bound in the blood and, therefore, could undergo glomerular filtration, they would be passively reabsorbed through the renal tubular cell down a concentration gradient. Several metabolic pathways are present to convert these agents to more water-soluble metabolites, which are generally less active than the parent compound, although there are several important exceptions.

Phase 1 metabolism involves the mono-oxygenase system in the smooth endoplasmic reticulum of the hepatocyte. Here, a variety of subtypes of cytochrome P450 enzymes (CYP450) catalyse oxidation, reduction, hydrolysis and dealkylation reactions. These enzymes are not specific, and drugs may compete with each other for metabolism via one particular pathway and a given drug may be metabolized via several routes mediated by several subtypes of CYP450. Some of the most clinically relevant subtypes and substances for which they are quantitatively important metabolic pathways are shown in Table 2.3.

Phase 2 metabolism involves the conjugation of parent drug or metabolite with a water-soluble molecule such as glucuronic acid (glucuronidation), sulphate, amino acid (such as glutathione or glycine) or acetyl coenzyme A (acetylation). As with phase 1 reactions, the metabolites are generally less active and, therefore, of low toxicity. However, there are important exceptions.

Finally, drugs with a high molecular weight (e.g. rifampicin) may be excreted in the bile, particularly as conjugates. The drug or its conjugate may be reabsorbed, either directly or after deconjugation by intestinal microflora, resulting in an enterohepatic recycling, which offsets the effects of biliary excretion. In obstructive jaundice the enterohepatic circulation is impaired, leading to an accumulation of drugs excreted in the bile (e.g. rifampicin and fusidic acid).

In liver disease, phase 1 metabolism is often relatively more affected than phase 2 metabolic reactions. The effect of liver disease is most marked for those drugs that are normally efficiently removed by hepatic metabolism (high-clearance compounds). These agents normally have high presystemic (first pass) metabolism, resulting in low bioavailability after oral administration despite complete absorption. Important examples include morphine, nifedipine and propranolol. Not only is the metabolic activity of the liver affected in liver disease, but also the intra- and extra-hepatic shunting results in a smaller proportion of the drug being metabolized on its first passage through the liver.

There is no ideal marker of the likely reduction in drug metabolic processes in chronic liver disease. The simplest clinical marker is the serum albumin, although strictly speaking
this is a marker of biosynthetic rather than metabolic function. Although the serum albumin gives a measure of the likely degree of liver damage and also of the patient’s prognosis, it is relatively crude. However, serum bilirubin, transaminase enzymes and alkaline phosphatase may be normal, even in the presence of severe chronic liver dysfunction, and may therefore be unhelpful. In acute liver damage, the albumin concentration may be normal at first because of the long half-life of the protein (20 days) and the reduction in vitamin K-dependent clotting factors, particularly factor XII, which has a half-life of 4 h, is a more useful guide. The International Normalized Ratio (INR), a derivative of the one-stage

<table>
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<tr>
<th>Cytochrome P450 subtype</th>
<th>Some important substrates</th>
<th>Some important inhibitors</th>
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<tr>
<td>CYP1A2</td>
<td>Clozapine</td>
<td>Cimetidine</td>
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<td></td>
<td>\textit{R}-Warfarin</td>
<td>Ciprofloxacin</td>
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<td></td>
<td>Tacrine</td>
<td>Erythromycin</td>
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<td></td>
<td>Theophylline</td>
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<tr>
<td>CYP2C9</td>
<td>Amitriptyline</td>
<td>Amiodarone</td>
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<tr>
<td></td>
<td>Phenytoin</td>
<td>Cimetidine</td>
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<tr>
<td></td>
<td>\textit{S}-Warfarin</td>
<td>Fluconazole</td>
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<td>Metronidazole</td>
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<td></td>
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<td>Sulphapyridine</td>
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<tr>
<td>CYP2C19</td>
<td>Diazepam</td>
<td>Fluoxetine</td>
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<td></td>
<td>Mephenytoin</td>
<td>Fluvaxamine</td>
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<td></td>
<td>Omeprazole</td>
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<tr>
<td>CYP2D6</td>
<td>Codeine</td>
<td>Amiodarone</td>
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<td></td>
<td>Haloperidol</td>
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<td></td>
<td>Imipramine</td>
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<td>Venlafaxine</td>
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<tr>
<td>CYP2E1</td>
<td>Ethanol</td>
<td>Disulfiram</td>
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<td></td>
<td>Isoniazid</td>
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<td>Paracetamol</td>
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<tr>
<td>CYP3A4</td>
<td>Astemizole</td>
<td>Cimetidine</td>
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<tr>
<td></td>
<td>Carbamazepine</td>
<td>Clarithromycin</td>
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<td></td>
<td>Corticosteroids</td>
<td>Erythromycin</td>
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<td></td>
<td>Ciclosporin</td>
<td>Grapefruit juice</td>
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<td></td>
<td>Erythromycin</td>
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<td></td>
<td>Lidocaine</td>
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<td>Nifedipine</td>
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<td></td>
<td>Terfenadine</td>
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<td>Verapamil</td>
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prothrombin time that is particularly sensitive to changes in factor VII, is normally used for this purpose.

In cardiac failure, cardiac output (normally around 6 l/min) is reduced. This results in a disproportionate reduction in hepatic blood flow (normally around 1.5 l/min) and a reduction in the systemic clearance of compounds that are normally efficiently cleared (e.g. lidocaine) for which hepatic blood flow is a major determinant of clearance. In addition, the liver can be affected by the increased venous back-pressure caused by failure of the right side of the heart consequent to left ventricular failure (biventricular or congestive heart failure). This results in increased size and congestion of the liver and derangement of liver function, which can progress in severe cases to jaundice.

Drug metabolism can decrease so that clearance even of drugs that are normally poorly cleared (e.g. theophylline) may be further decreased. In addition, the increased venous pressure may result in intestinal mucosal oedema and reduced absorption of relatively inefficiently absorbed drugs (e.g. furosemide).

**Extremes of age**

**Neonates**  The neonatal period covers the first 30 days of life. Prematurity amplifies many of the problems encountered in the drug treatment of this group, but even the healthy full-term neonate is prone to ADRs because of the immaturity of pharmacokinetic processes (Routledge, 1994). Absorption of drugs may be more complete in the neonate as transit delays are compensated for by increased mucosal contact times. If a rapid drug response is needed, then routes other than the oral route should be used. Reduced gastric acidity may result in increased absorption of drugs, such as with amoxycillin. Reduced body fat and increased body water result in changes in the volume of distribution for lipid- and water-soluble drugs.

Other influences include reduced plasma albumin and alpha-1-acid glycoprotein (AAG) concentrations, resulting in reduced plasma protein binding affinity and increased competition for binding from free fatty acids and bilirubin. These effects tend to prolong the half-life of the drug. Despite increased hepatic size relative to body size, phase 1 (and most phase 2) metabolic enzyme systems are immature, so hepatic metabolism of drugs may be reduced. Chloramphenicol produces the ‘grey baby’ syndrome via inefficient glucuronidation for example. Renal function is globally reduced in neonates, with the GFR being about 40 per cent of the normal adult value. This results in delayed excretion of drugs such as digoxin and gentamicin. In general, smaller weight-related doses of all drugs are required in the neonatal period (Rylance and Armstrong, 1997).

**The elderly**  The increased risk of ADRs in the elderly is well described, and around 10 per cent of all admissions to geriatric units are directly due to an ADR, generally a type A reaction (Williamson and Chopin, 1980).

Pharmacokinetic factors are important contributors to the increased risk of type A ADRs in the elderly. The GFR tends to decline with increasing age from 30 years onwards (Lindeman, 1992) so that the average GFR of an 80-year-old is 30 per cent less, even in the absence of overt renal disease. This decline does not occur in all elderly subjects and may be partly related to underlying pathophysiological changes rather than the inevitable consequence of age. Nevertheless, the decline in renal function is important in relation to renally excreted drugs with a low therapeutic index, as mentioned above. The relationship between
age and drug metabolism is less clear-cut. There does tend to be a slow decline in the metabolism of some drugs with increasing age, but wide variability at any age indicates that factors other than chronological age are more important determinants of the rate of metabolism. Perhaps the most important of these is the presence of physical frailty (Owens et al., 1994). Biological (rather than chronological) age more accurately reflects nutritional state and protein energy malnutrition. This is particularly seen in the housebound or nursing home resident and is associated with a reduction in the activity of several important pathways of drug metabolism (O’Mahony and Woodhouse, 1994).

Pharmacogenetic factors

Genetic factors play a major role in determining drug response and handling, as well as in susceptibility to ADRs. Although receptors, transport processes and metabolic pathways may all be affected, most is known about the metabolic processes, many of which are responsible for handling foreign substances (xenobiotics), of which drugs are an important group. Allelic variations affecting drug handling (pharmacokinetics) with a frequency of at least 1 per cent are often termed polymorphisms (e.g. acetylation), whereas less common variants are often classified as rare inborn errors of metabolism (e.g. porphyria), but the distinction is relatively arbitrary.

The extent to which an individual metabolizes a drug is often, if only partly, genetically determined. Twins derived from the same ovum (monozygotic) metabolize many drugs at a similar rate, whereas dizygotic twins differ more in clearance values. For most drugs the variability in metabolism is unimodally distributed. A bimodal or trimodal distribution may suggest the existence of separate populations capable of metabolizing those drugs at markedly different rates. Some pathways of drug metabolism showing such polymorphism are acetylation, oxidation, succinylcholine hydrolysis (de-esterification) and thiopurine S-methylation. These issues are discussed in detail in recent reviews by Ingelman-Sundberg et al. (1999), Meyer (2000) and Weinshilboum (2003). Polymorphisms affecting drug target genes, and gene products other than drug metabolizing enzymes (e.g. receptors) or disease-modifying or treatment-modifying genes that can influence drug response, are reviewed by Evans and McLeod (2003). However, the clinical significance of these polymorphisms to the risk of ADRs is generally less well studied than polymorphisms affecting drug metabolism.

Acetylation

This metabolic pathway with its polymorphic distribution was discovered over 40 years ago. The enzyme N-acetyltransferase mediates acetylation of some drugs. At least two populations exist with different rates of acetylation. The gene controlling the N-acetyltransferase in the liver (NAT2) is on chromosome 8 and the slow phenotype is inherited as an autosomal recessive trait. For reasons that are not clear, the proportion of slow acetylators varies markedly between different races, being 55 per cent in European Caucasians, 10 per cent in Japanese and 5 per cent in the Inuit of northern Canada and in Egyptians. Drugs that undergo genetically determined acetylation are dapsone, isoniazid, hydralazine, phenelzine, procainamide and some sulphonamides, such as the sulphapyridine, which forms part of the sulphasalazine molecule used for the treatment of ulcerative colitis. Slow acetylators require lower doses of hydralazine than fast acetylators in the treatment of hypertension and are more likely to have dose-related toxicity with high doses of sulphasalazine. They are also
more likely to develop the lupus erythematosus-like syndrome caused by isoniazid or hydralazine, and the pyridoxine-deficient peripheral neuropathy caused by isoniazid. Phenytoin toxicity due to inhibition of its metabolism by isoniazid occurs more frequently in slow acetylators receiving isoniazid for treatment or prophylaxis of tuberculosis. Drug-related lupus (DRL) is very rarely seen in fast acetylators of hydralazine, but not all slow acetylators develop the complication. It is clear, therefore, that the mechanism is multifactorial, and several studies have examined other causes of susceptibility. Studies of human leucocyte antigen (HLA) associations with DRL have given conflicting results, but immunogenetic differences are associated with systemic lupus erythematosus and it is likely that they will also pertain to the drug-induced form of this condition. The acetylator status of an individual may be easily assessed by giving isoniazid (200 mg orally) and measuring the ratio of the concentration of acetylsisoniazid and isoniazid in a plasma or saliva sample 3 h later (Hutchings and Routledge, 1986). Genotyping only requires a sample of blood without administering a drug and may be available for clinical use in the future.

**Oxidation**

Certain metabolic pathways involving oxidation are polymorphically inherited, with poor and extensive metabolizer phenotypes.

**CYP2D6** One of the most important examples is the autosomal recessive defect of cytochrome P450, CYP2D6. The gene is located on chromosome 22 and the poor metabolizer phenotype is inherited in an autosomal recessive fashion. This phenotype occurs in about 7 per cent of Caucasians and up to 20 per cent of Ethiopians, but has a lower prevalence in other racial types (e.g. 1 per cent in Oriental populations). It affects the metabolism of codeine, debrisoquine, haloperidol, imipramine, paroxetine and several other antidepressants, phenformin, propafenone and several other antiarrhythmic agents, sertaline, metoprolol and several other beta adrenoceptor blocking drugs, and up to 100 other drugs. The dose-related adverse effects of some of these drugs (e.g. peripheral neuropathy with perhexiline and central nervous system (CNS) toxicity with some tricyclic antidepressants) are more likely in poor hydroxylators. Quinidine inhibits this pathway, and its concurrent administration may result in a genotypically extensive metabolizer behaving as a poor metabolizer.

The lactic acidosis that has been described in approximately 10 per cent of subjects receiving phenformin was first reported in 1959, 10 years before the drug was marketed in the UK (Walker and Linton, 1959). The drug was not withdrawn until around 1980, after approximately 50 fatal case of lactic acidosis associated with its use had been reported. Despite this, phenformin is still used in some countries outside the USA and Europe and lactic acidosis is still reported.

Prolongation of the QT interval of the electrocardiogram (and increased risk of torsades de pointes and other serious ventricular arrhythmias) may be commoner in poor metabolizers of certain neuroleptic drugs (e.g. thioridazine and droperidol) by this pathway. This has resulted in licence variations (or voluntary drug withdrawal) in some countries. It is discussed later in this chapter. Ultrarapid metabolism may also rarely occur via this pathway due to gene amplification in some subjects, and failure of antidepressant therapy has been associated with this abnormality (Bertilsson et al., 1993).
CYP2C9  The metabolism of the most potent enantiomer of warfarin, S-warfarin is predominantly via hydroxylation, mediated by CYP2C9. Individuals requiring low doses of warfarin to provide adequate anticoagulation are more likely to be poor metabolizers, because they possess a variant allele CYP2C9*2 or CYP2C9*3 rather than the wild-type allele CYP2C9*1. It has been suggested that such individuals may be at increased risk of warfarin-induced bleeding (Aithal et al., 1999), although this has been disputed (Taube et al., 2000). They also have lower clearance values of the anticonvulsant diphenylhydantoin (phenytoin), which is also metabolized largely by this route (van der Weide et al., 2001).

CYP2C19  The metabolism of mephenytoin (an anticonvulsant drug similar to phenytoin) and the proton pump inhibitor omeprazole is mediated by cytochrome CYP2C19, whose activity is bimodally distributed. The normal (wild-type) gene is absent in 2–6 per cent of Caucasians and up to 20 per cent of Southeast Asians (Japanese, Koreans and Chinese) in an autosomal recessive inheritance, and these people are therefore poor metabolizers. These individuals are more likely to develop drowsiness during mephenytoin treatment, but they may have better eradication rates when omeprazole is used in combination with amoxycillin in the treatment of gastrointestinal *Helicobacter pylori* infection (Furuta et al., 1998).

**Succinylcholine de-esterification**

Succinylcholine is a depolarizing neuromuscular blocking agent used in induction of general anaesthesia. Normally, it is rapidly metabolized in the plasma by a non-specific esterase called pseudocholinesterase (butyrylcholinesterase) and has a short half-life and duration of action. Some individuals possess pseudocholinesterase of abnormal affinity or amount, and metabolize the succinylcholine much more slowly, resulting in a prolonged neuromuscular blockade. Prolonged apnoea was first recognized in 1953 (Forbat et al., 1953). It is now known that there are three types of abnormality of pseudocholinesterase, each inherited in autosomal recessive fashion: the dibucaine-resistant, fluoride-resistant and gene types (Kalow and Genest, 1957). The prevalence of the homozygous poor metabolism phenotype is only 1 in 3500 in Europeans, so it is not a common polymorphism like acetylation or CYP2D6 oxidation. The gene for the trait is located on chromosome 3.

In some individuals there is an increase of up to threefold in the concentration of plasma pseudocholinesterase with consequent resistance to the effects of succinylcholine (Cynthiana variant). The prevalence may be as high as 1 in 1000 (i.e. three times more frequent than the deficiency state).

**Thiopurine S-methylation**

Thiopurine methyltransferase (TPMT) is one of three major enzymes responsible for the metabolism of azathioprine, via its active metabolite 6-mercaptopurine to 6-methylmercaptopurine. TPMT activity is determined by an allelic polymorphism for either high (TPMT H) or low (TPMT L) enzyme activity. Homozygotes for the low activity allele (0.3 per cent of the population) are known to be at risk of profound myelosupression on recommended doses of azathioprine and heterozygotes (11 per cent) may also be at risk. In such individuals, more drug is metabolized via one of the other pathways (mediated by hypoxanthine guanine phosphoribosyl transferase) to toxic 6-thioguanine nucleotides. On the other hand, homo-
zygotes for the high TPMT activity allele may be inadequately immunosuppressed with conventionally recommended doses of this drug. The gene is located on chromosome 6.

**Pharmacodynamic risk factors**

In general, many of the groups with pharmacodynamic reasons for susceptibility to ADRs are also those with pharmacokinetic differences. In addition, pharmacogenetically determined differences in pharmacodynamics may increase the risk of adverse reactions.

**Renal disease**

In renal failure, there is an accumulation of toxic waste products, resulting eventually in severe uraemia and encephalopathy with confusion, loss of memory and other neurological signs. It is thought that purine metabolites, amines, indoles, phenols and other substances may contribute to uraemia, and retained middle molecules (molecular weight 500–5000 Da) may also contribute to the problem. It is likely that subclinical accumulation may contribute to the increased sensitivity to psychoactive drugs, particularly opiates, although pharmacokinetic factors may also be important for several drugs.

**Liver disease**

Encephalopathy may occur in severe liver disease. Even before this, however, a subclinical phase may be detected by psychometric or electrophysiological testing. It is thought to be due to decreased hepatic extraction of substances that tend to inhibit neuronal function. The precise mechanism by which psychoactive drugs cause a further deterioration of cerebral function in these circumstances is not yet known; however, in the case of benzodiazepines it is thought to be related to an interaction at the GABA receptor complex. Liver disease (both acute and chronic) is associated with a reduced production of vitamin K-dependent clotting factors, even after parenteral vitamin K administration. This (together with other defects of haemostasis) contributes to an increased risk of bleeding *per se*; in addition, bleeding risk due to drug therapy (e.g. aspirin and other NSAIDs) is increased. The increased sensitivity to warfarin is caused by a combination of this effect and the reduced clearance of warfarin in liver disease, although the pharmacodynamic sensitivity is probably the more important factor.

**Sex**

Females appear to be more susceptible to ADRs than males (Hurwitz and Wade, 1969; Hoigné *et al*., 1984; Jacubeit *et al*., 1990; Bowman *et al*., 1996), with a study by Domecq *et al*. (1980) giving figures of 37.9 per cent for women and 29.6 per cent for men. This remained the case even after due consideration of the duration of hospitalization, number of drugs, age, and the presence of liver and renal disease. The increases may be due to pharmacokinetic factors (women tend to have lower ratios of lean body mass to adipose tissue mass) and hormonal influences, e.g. tardive dyskinesia (Kando *et al*., 1995). In seven phase-1 studies, females reported spontaneously 2.3 times more frequently than males, and side effects due to laboratory abnormalities were higher in women (26 per cent) than in men (15 per cent; Vomvouras and Piergies, 1995). There may also be differences in pharmaco-
kinetics (e.g. serum propranolol levels are twice as high in women as in men; Walle et al., 1994). Androgens and oestrogen affect the QT interval and women are more prone to torsades de pointe (Drici and Clement, 2000). Female patients are estimated to have a 1.5- to 1.7-fold greater risk of developing an ADR than are male patients (Heinrich, 2001). Eight out of ten prescription drugs withdrawn during the period 1997 to 2001 posed a greater risk for women than for men (White, 1999).

**Extremes of age**

**Neonates** The blood–brain barrier regulates the entry of drugs to the brain. It is less efficient at birth, especially in preterm neonates, who are particularly sensitive to psychoactive agents such as opiates or lithium.

**Elderly** Increasing age is associated with several pharmacodynamic changes that may increase the risk of drug toxicity. Lamy (1991) has classified these as:

- primary (physiological) ageing factors
- secondary (pathophysiological) ageing factors
- tertiary (psychological) ageing factors.

All these factors may affect response. Primary factors include the slower metabolic processes, the reduction in brain mass, neurone density, cerebral blood flow and capacity for autoregulation, and possible increased permeability of the blood–brain barrier, all of which occur with increasing age. Secondary factors include the many diseases to which the elderly are more prone. Tertiary factors include the effects that psychological stresses may have upon motivation, nutrition and other aspects of self-care. Physiological ageing of the CNS contributes to the increased risk of toxicity of drugs acting on the CNS. Reduced ability to respond to stress (reserve capacity) results in reduced ability to maintain homeostasis, so that drugs that affect balance (e.g. CNS sedatives), temperature regulation (e.g. phenothiazines), bowel and bladder function (e.g. anticholinergic agents) and blood pressure (e.g. vasodilators) may all cause adverse effects at normal adult doses.

**Risk factors for type B reactions**

Type B reactions are ‘bizarre’, in that they cannot be predicted from the drug’s known pharmacology. They include allergic reactions to drugs, and because of their often dramatic onset may be associated with a proportionately higher mortality than type A reactions, although they are less common. Type B reactions may occur to the excipients, preservatives or vehicle in the formulation. This problem is discussed at length by Uchegbu and Florence (1996). In the case of L-tryptophan-associated eosinophilia-myalgia syndrome, an unidentified contaminant occurring during the production of one formulation may have been responsible (Kilbourne et al., 1996). The mechanisms of type B reactions are often poorly understood, but many involve allergic or pseudoallergic mechanisms (Rieder, 1994).
Allergic reactions

Allergic reactions to drugs are often known as hypersensitivity reactions.

Type I hypersensitivity

The commonest form of hypersensitivity is the immediate hypersensitivity associated with hay fever and asthma. This was classified by Gell and Coombs as type I (or immediate) hypersensitivity, and certain drugs (e.g. penicillins and cephalosporins) can also cause this problem. Mast cells, which are common in the gut and lung, and basophils have a high affinity receptor for the Fc domain of the immunoglobulin (IgE). When two such IgE molecules bound together as a dimer on the cell wall are crosslinked by a previously circulating antigen molecule, mediators such as histamine, leukotrienes and prostaglandins are released. If these are released in large amounts, then systemic anaphylaxis may ensue, with bronchospasm and circulatory collapse, sometimes with fatal consequences.

Type II hypersensitivity

In type II, or antibody-mediated cytotoxic hypersensitivity, the antigen (rather than the antibody as in type I reactions) is bound to the surface of a cell membrane, often a red cell or platelet. Circulating immunoglobulin (IgG, IgM or IgA) reacts with the antigen to stimulate complement as well as cytotoxic cells, resulting in lysis of the target cell. This is the mechanism of certain drug-induced haemolytic anaemias (e.g. due to methyldopa) and thrombocytopenias (e.g. due to quinine).

Type III hypersensitivity

In type III hypersensitivity reactions, antigen–antibody complexes are deposited in areas of turbulent flow or filtration (e.g. the glomerulus of the kidney). This type of reaction, known as immune complex hypersensitivity, results in complement activation and the lysosomes released by polymorphonuclear cells cause vascular damage. In addition to glomerulonephritis, this reaction may result in fever, lymphadenopathy, arthritis and rashes and may be induced by several drugs, including gold and penicillamine.

Type IV hypersensitivity

Type IV, or delayed-type (cell-mediated) immunity, occurs in the absence of detectable circulating antigen or antibody. Specific helper T lymphocytes may be stimulated by a drug that acts as a hapten and has complexed with a tissue macromolecule to form an antigen. This results in the release of cytokines and the accumulation of other cells (particularly monocytes) in the area, and resulting granulomata, oedema or widespread rash, normally several days after exposure to the drug. It appears that people with human immunodeficiency virus (HIV) infection may be more prone to such drug-induced allergic reactions, particularly in response to sulphonamides.
Pseudoallergic reactions

Pseudoallergic reactions are so called because they mimic allergic hypersensitivity, particularly of type I hypersensitivity. Such reactions, if severe, are often termed anaphylactoid and can occur on first exposure to a drug, particularly a neuromuscular blocker or radiographic contrast dye. It is not known why certain individuals are predisposed to such reactions, but asthmatics, especially those with nasal polyps, are more likely than others to experience such reactions with aspirin, for example. There is cross-reactivity with other NSAIDs and with tartrazine, a dye that was once commonly used in drugs but which is now restricted in use.

Drug metabolism and type B adverse drug reactions

As well as its role in type A toxicity, drug metabolism may have an important role in determining type B ADRs. Although metabolism generally results in detoxification of a drug, it may sometimes produce chemically reactive metabolites in a process termed bioactivation (Pirmohamed et al., 1996). If the body’s defence mechanisms against this metabolite are overwhelmed, or repair processes are inadequate, then it can combine with tissue macromolecules (e.g. protein or DNA) to cause toxicity, either directly or via activation of immune processes. The risk of this occurring is determined by a variety of factors, including age, gender, HLA status and a variety of still unrecognized host-dependent factors. For this reason, type B toxicity caused by bioactivation is still unpredictable in most cases.

Pharmacogenetic factors

Glucose-6-phosphate dehydrogenase deficiency

Some individuals have erythrocytes that are genetically deficient in glucose-6-phosphate dehydrogenase (G6PD), which is at least partly responsible for preventing the oxidation of various red-cell proteins. Haemolysis occurs if the abnormal erythrocyte is exposed to oxidizing agents, probably because of unopposed oxidation of sulphhydryl groups in the cell membrane. Common causative agents include aspirin, sulphonamides, some antimalarials, antileptotics and pharmacological doses of vitamins K or C. The gene is on the X chromosome, and inheritance of the deficiency state therefore occurs in a sex-linked (X) recessive mode. It is relatively common (up to 14 per cent) in African Americans and in Mediterranean races, but the severity of reactions appears to be greater in G6PD-deficient Caucasians.

Porphyria

People with hepatic porphyrias (acute intermittent porphyria or porphyria cutanea tarda) have abnormalities of haem biosynthesis and symptoms may be precipitated by many drugs, particularly alcohol, the oral contraceptive, barbiturates and sulphonamides. (For a fuller and up-to-date list, contact the Welsh Medicines Information Centre, University of Wales, Cardiff CF14 4XW, UK, tel.: +44 (0)2920 742979).
**Malignant hyperthermia**

This is a serious and occasionally fatal condition that may occur in association with general anaesthesia with halothane or methoxyflurane used in conjunction with succinylcholine. It occurs in about 1 in 20,000 anaesthetized patients and is inherited in an autosomal dominant fashion. Body temperature may rise to 41°C with increased muscle tone, tachycardia, sweating, cyanosis and tachypnoea. Creatine kinase activity may rise due to muscle damage, and muscle death (rhabdomyolysis) may occur. The muscle relaxant, dantrolene, and diazepam, which acts as a general relaxant, are sometimes effective in preventing muscle damage. The gene is thought to lie on the long arm of chromosome 19.

**Coumarin resistance**

Coumarin resistance is a very rare defect that has been reported in only two human kindreds. In this condition, up to 20 times the usual dose of warfarin or other coumarin anticoagulant may be required to produce satisfactory anticoagulation. It has an autosomal dominant inheritance and the mechanism appears to be resistance of the enzyme vitamin K epoxide reductase in the vitamin K–K epoxide shuttle to the normal inhibitory effect of coumarins. The site of the gene is not known.

**Aminoglycoside antibiotic-induced deafness**

Susceptibility to the ototoxic effects of aminoglycoside antibiotics, such as gentamicin, may be genetically determined in some individuals. The prevalence is thought to be at least 1 in 10,000, and in Shanghai it is thought that 25 per cent of all deaf mutes may have become deaf after exposure to these widely used agents (Hu et al., 1991).

Inheritance is solely through the maternal line, and both sexes are equally affected, supporting the evidence that transmission is dependent upon the mitochondrial genome, a rare mechanism for inheritance of disease. Recently, the 1555A → G mitochondrial mutation has been shown to be associated with a susceptibility to aminoglycoside antibiotics. It has been found in 3 per cent of outpatients with hearing problems, making it the most prevalent mitochondrial mutation found in the hearing-impaired population (Usami et al., 2002).

**Long QT syndrome**

This condition is characterized by an increased delay between the QRS complex and T wave in the electrocardiogram associated with a susceptibility to life-threatening ventricular arrhythmias, such as *torsades de pointes* (Figure 2.1), which may progress to ventricular

![Figure 2.1](image-url) An electrocardiogram showing *torsades de pointes*
fibrillation in 20 per cent of cases. In addition, sudden death may be described more commonly in individuals with long QT syndrome. QT interval prolongation may occur spontaneously or during therapy with some drugs (e.g. some antihistamines, antiarrhythmic drugs, neuroleptics and tricyclic antidepressants). Congenital long QT syndromes are associated with mutations in the genes encoding potassium or sodium channels, which mediate the depolarization of cardiac conducting tissue. There seems to be several forms of the condition, with linkages between chromosomes 3, 7 and 11 in three of these. Clinical syndromes caused by these phenotypes include the Romano–Ward and Jervell–Lange-Neilsen syndromes. The recently described Brugada syndrome is an important cause of sudden death in Southeast Asia and is caused by a mutation in a sodium channel (Roberts and Brugada, 2003). The QT interval duration and morphology are not always very sensitive, and specific diagnostic markers (and the penetrance of some of the mutations) may not be great, making the identification of affected individuals and carriers difficult.

The list of drugs that may prolong the QT interval continues to increase, and an up-to-date list is available at http://www.torsades.org/. It is not known how many cases of severe ventricular arrhythmias are related to an excessive concentration of the drug, since toxicity appears to be type A in nature. In addition, the presence of known risk factors, e.g. underlying bradycardia, hypokalaemia, hypomagnesaemia, female gender (two- to four-fold increased risk), recent conversion from atrial fibrillation to sinus rhythm, or the presence of left ventricular hypertrophy, may markedly increase the risk. These factors are of particular concern in those with underlying congenital long QT syndromes caused by abnormalities in ‘channelopathy genes’, so that many cases are likely to be multifactorial in nature. Many of the drugs causing QT prolongation are CYP3A4 substrates, whose physicochemical characteristics mean that they may also affect the rapid inward potassium channel (Ikr or HERG) in cardiac conducting tissue. Others are CYP2D6 substrates, which may have homology in sometimes also affecting the inward sodium channel (INa).

Genetic predisposition to adverse drug reactions

Factors associated with an increased risk of ADRs include a history of allergic disorders, such as atopic disease or hereditary angioedema (Grahame-Smith and Aronson, 1992). HLA status may also be important:

- The risk of nephrotoxicity from penicillamine is increased in patients with the HLA types B8 and DR3, whereas patients with HLA-DR7 may be protected.

- The risk of skin reactions with penicillamine is associated with HLA-DRw6, and the risk of thrombocytopenia is associated with HLA-DR4; patients with HLA-DR4 also have a greater risk of the lupus-like syndrome (see above) associated with hydralazine.

- The risk of a hypersensitivity reaction to the HIV-1 reverse transcriptase inhibitor abacavir is associated with HLAB5701, HLA-DR7 and HLA-DQ3 (Mallal et al., 2002).
Detection of adverse drug reactions

Vere (1976) described the tendency of ADRs to masquerade as natural illness over 25 years ago. He gave five main reasons why so many adverse reactions escape unnoticed:

- The reaction may be so odd or bizarre that an often used and apparently innocent drug escapes suspicion.
- The drug-induced disorder can closely mimic a common natural disease.
- There is a long delay in the appearance of the adverse effect.
- The drug evokes a relapse of natural disease or may evoke a disorder in a naturally susceptible subject.
- The clinical situation may be so complex that its drug-related components pass unnoticed.

Even today, iatrogenic disease may still go unrecognized. If the delay in onset of iatrogenic disease is very prolonged, then the effects are even more difficult to detect. Autoimmune haemolytic anaemia has been described 9 years after uneventful antihypertensive treatment with methyldopa for example (Terol et al., 1991), so continued vigilance is required in all patients throughout the course of their treatment.

Another difficulty in identifying drug-induced disease is that there may be a significant prevalence of the non-drug-induced condition in the community. Vere (1976) pointed out that the risk of adenocarcinoma of the vagina in female children born to mothers who took high doses of the oestrogen stilboestrol in pregnancy was probably recognized largely because it was so unusual that there was no ‘background noise’. The same argument applies to the unusual maldevelopment of limbs seen in phocomelia caused by thalidomide, which was therefore recognized reasonably quickly.

Drugs that aggravate already existing disease may escape suspicion for some time, particularly if the natural disease is common. Fialuridine is a nucleoside that was undergoing trials for the treatment of hepatitis B. Unfortunately, the major adverse effect of this drug was on the liver, and the worsening liver function in treated patients appeared to be explained by the monitoring physicians as worsening of the hepatitis rather than as direct drug toxicity. The incorporation of the nucleoside in patients into the cell nuclear protein ensured that the toxicity was quite persistent, even after withdrawal of the drug, and several patients died of the complications of lactic acidosis associated with the hepatitis (McKenzie et al., 1995).

Finally, ADRs may be difficult to detect because of the confounding effects of other treatments being administered at the same time. Some agents (e.g. blood products or contrast media) may be administered for therapeutic or diagnostic purposes while the patient is undergoing treatment, and other drugs (e.g. corticosteroids or antihistamines) may affect the natural history of iatrogenic disease and prevent it from being recognized.
Biochemical and histological confirmation

There are relatively few specific investigations to confirm the presence of an ADR. Biochemical pictures associated with iatrogenic disease may mimic those from other idiopathic causes. Histological evidence, although often difficult to obtain, may sometimes be more helpful:

- The ductopenia associated with flucloxacillin-induced liver damage is relatively specific for this drug-induced hepatic damage.
- Although not specific for drug-induced glomerulonephritis, the granular deposition of immune complexes shown on immunocytochemical stains of renal biopsy material contrasts with the more linear deposition seen in other forms of immune complex glomerulonephritis, such as Goodpasture’s syndrome.

Some in vitro investigations, such as the radioallergosorbent test (RAST), which detects antigen-specific antibodies in serum, or the histamine release test, may be valuable in determining anaphylactic or anaphylactoid reactions, particularly to anaesthetic induction agents. The histamine release test and basophil degranulation test may have an advantage over RASTs in that they will demonstrate anaphylactoid reactions (i.e. those that are non-IgE mediated) as well as those that are anaphylactic and mediated by IgE. Tryptase is the most important protein in mast cell granules and is released in anaphylactic as well as in anaphylactoid reactions. Plasma tryptase concentrations are maximal 1–6 h after the reaction, but may be detected in concentrations above normal for up to 12–14 h, making this test a useful but nonspecific confirmatory test in severe reactions, particularly those occurring in anaesthesia. Urine methylhistamine concentrations have also been used for this purpose, but they are more difficult to interpret (Association of Anaesthetists of Great Britain and Ireland and The British Society of Allergy and Clinical Immunology, 1995).

Tests using other cellular components of blood, such as the basophil degranulation test, passive haemagglutination, lymphocyte transformation and leukocyte/macrophage migration inhibition tests, may have some value in certain allergic type B reactions; however, the sensitivity of these tests is relatively poor, and negative tests do not always exclude the possibility of drug-induced disease (Pohl et al., 1988). The major difficulty with many of the in vitro tests is that the challenge agent is normally the parent drug. Since the responsible compound may be a metabolite or breakdown product, and unless this specific agent is present or generated in the in vitro situation, the test may be falsely negative (Pohl et al., 1988).

Skin testing and direct drug rechallenge

Skin tests are essentially a form of in vivo rechallenge at reduced drug dose. Such tests may be insensitive and nonspecific. In addition, they can be potentially dangerous, and deaths have been reported with intradermal testing to penicillin, for example, although this is rare with a careful technique and newer reagents. Scratch tests and intradermal tests may be particularly helpful in the investigation of immediate-type anaphylactic/anaphylactoid reactions to drugs used during anaesthesia. Skin patch testing may be helpful in the
investigation of fixed drug eruptions, but should not be used in Stevens–Johnson syndrome or toxic epidermal necrolysis (Breathnach, 1995).

Systemic drug rechallenge is fraught with even more potential risk than skin testing. It is generally only considered when a suspected drug is the only agent known to be effective in a particular condition (e.g. allopurinol in long-term prophylaxis of gout). Rechallenge with the protease inhibitor abacavir has, for example, resulted in severe (and sometimes fatal) reactions and is absolutely contraindicated (Hetherington et al., 2001).

Other evidence

Since direct evidence is often difficult to obtain, circumstantial evidence may be important in detecting ADRs. A useful criterion for determining whether a reaction is drug induced is the timing of the onset of the symptoms relative to the start of drug therapy:

- Type A reactions normally occur when the drug has accumulated; thus, it may take five half-lives of the drug for the ADR to reach maximum intensity.
- Type B reactions are often immunological in nature and so sometimes require a latent period of up to 5 days before being seen. Most occur within 12 weeks of initiation of drug therapy.

The time course for type B reactions may, however, be clouded by several factors. Drug-induced agranulocytosis, for example, may take two or more weeks to occur after initial drug exposure and may, therefore, present after the drug has been discontinued. The same is true of drug-induced jaundice, particularly when it occurs after the agent is used for short-course therapy (e.g. co-amoxiclav or flucloxacillin). Some type B reactions (e.g. halothane-induced jaundice) appear more rapidly on re-exposure after a previous reaction has occurred.

The time course to resolution after stopping the drug (dechallenge) may also be of help in assessing causality. Some ADRs take a considerable time to disappear after drug discontinuation, particularly if the drug has a long half-life of elimination (e.g. amiodarone), whereas others may be associated with irreversible effects (e.g. pulmonary fibrosis after busulphan or nitrofurantoin).

The absence of an alternative explanation is an important criterion in considering a drug-related cause, but the latter should still be considered and relevant information sought without waiting to rule out non-drug-related causes. Finally, it has been shown that doctors rely to a large extent on whether previous reports of ADRs have been published in association with the drug. It is important that clinicians are trained to have a much higher level of suspicion of the possibility of iatrogenic disease, since it is a situation in which prompt treatment (e.g. drug withdrawal) may result in a permanent cure.

Management of adverse drug reactions

Type A reactions will generally respond to a reduction in dose of the drug, although temporary drug discontinuation may be necessary if the reaction is significant. Unfortunately, some adverse effects are permanent (e.g. lung fibrosis with busulphan or liver fibrosis
with methotrexate), although withdrawal of treatment as soon as the condition is recognized may reduce the eventual magnitude of toxicity.

For type B reactions the clinician should withdraw the suspected drug immediately and refer the patient for specialist investigations (e.g. skin testing if appropriate) on recovery. It is sometimes necessary to give supportive therapy, particularly for anaphylactic and anaphylactoid reactions, and corticosteroids may sometimes be used to suppress inflammatory or potentially fibrotic processes.

In rare circumstances, when no alternative agents are available for treatment of a particular condition, desensitization by administration of gradually increasing doses of the drug may eventually allow the patient to tolerate the agent at full dose. This approach has been used successfully in some patients with aspirin or allopurinol hypersensitivity, for example.

Part of the management of ADRs is to report them to the regulatory authorities. This allows the appropriate bodies to assess the risk–benefit of particular medications, which can contribute to safe drug use in susceptible subjects in the future. In the UK, the Committee on Safety of Medicines (CSM) (Medicines and Healthcare products Regulatory Agency, MHRA) asks health professionals to report all suspected serious reactions to established medicines and all suspected adverse reactions to newly introduced (the so-called black triangle '▽') drugs, whatever their severity.

**Prevention of adverse drug reactions**

The goal of therapeutics is to obtain optimum efficacy and minimum toxicity of drug therapy. This ideal is difficult to achieve because of the wide variability in drug response within patients. Bespoke prescribing aims to achieve this by tailoring initial doses to the individual patient and titrating drug dose subsequently to avoid toxicity. Bespoke prescribing has been used for the initiation of warfarin and heparin therapy (Routledge, 1986). The approach is primarily of value in avoiding type A adverse reactions, although the avoidance of excessive doses of certain drugs in high-risk individuals may also reduce the risk of type B reactions (e.g. there is a higher risk of severe allergic-type skin reactions with excessive doses of allopurinol in patients with renal disease).

In renal dysfunction, the creatinine clearance is closely related and similar in magnitude to the GFR. Thus, GFR can be calculated by measuring the patient’s serum creatinine (which has little diurnal variation) and age, gender and body weight. The Cockcroft–Gault equation uses the relationship:

\[
\text{Creatinine clearance} = \frac{(140 - \text{age (y)}) \times \text{Body weight (kg)}}{0.82 \times \text{Plasma creatinine} (\mu\text{mol/l})}
\]

For females, who have less muscle mass at any given weight, the result must be multiplied by 0.85. This equation is relevant only when the renal function is relatively constant and in the absence of concomitant liver disease. It is a useful guide to dose adjustment in renal disease and in the elderly when glomerular filtration is the major renal excretory mechanism. The proportional dose adjustment will also depend upon the proportion \( F \) of the drug excreted unchanged by the kidney (since some drug may be cleared by metabolic pathways) in the following formula:
Dose (as proportion of normal) = \frac{(1 - F) + F \times GFR \text{ (patient)}}{GFR \text{ (normal)}}

This relationship can be used to aid in the calculation of the dose of digoxin or gentamicin, for example. The situation is more difficult if renal tubular secretion is a major excretory mechanism, since no clinically applicable direct measurement of this pathway is available.

Dose adjustment is more difficult in liver disease, although the serum albumin concentration is of some help in deciding upon the starting dose. The initial induction dose of warfarin should be reduced by at least 50 per cent if the INR is greater than 1.3 (Fennerty et al., 1988).

**Therapeutic drug monitoring**

Monitoring drug concentration in the plasma is also of value in avoiding some ADRs. The ideal way to monitor drug therapy is to have a simple measure of drug effect (e.g. oral anticoagulant therapy), but this is rarely available. In the absence of a pharmacodynamic measure, and particularly when the only endpoint is the absence of features of the illness (e.g. absence of seizures during anticonvulsant treatment or arrhythmias during antiarrhythmic treatment), the plasma drug concentration is a useful surrogate marker of efficacy and safety. To be applicable, the drug should have a concentration-related and reversible effect without the development of tolerance, and the metabolites should be relatively inactive unless active metabolite concentrations are also measured. Relatively few drugs fulfil these strict criteria, but therapeutic drug monitoring (TDM) is used to adjust the doses of ciclosporin, digoxin, gentamicin and other aminoglycoside antibiotics, lithium, phenytoin (diphenylhydantoin) and theophylline (Routledge and Hutchings, 2001).

Since drugs are normally given at fixed intervals, the plasma concentration varies between doses during the processes of absorption, distribution, metabolism and excretion. Samples taken some time after the dose are therefore more reflective of the average concentration between doses and should be taken at least 8 h after digoxin administration and 12 h after lithium. Peak levels are sometimes required (e.g. with gentamicin) and occur around 30—60 min after an intramuscular injection or immediately at the end of an intravenous infusion. Peak levels of orally administered drugs are achieved at 30—180 min after conventional formulations and later after modified-release preparations. For many drugs, a sample taken just before the next dose is due (trough concentration) will correlate best with the average (steady-state) concentration.

It takes approximately five half-lives before the plasma concentrations of a drug reach their maximum steady state level. Sampling before this time has elapsed is therefore most valuable if drug toxicity due to excessive accumulation is expected. Ideally, five half-lives should elapse before steady-state plasma concentrations are measured, but this may take some time in certain cases (e.g. 9 months in the case of amiodarone, which has a half-life of 45 days). Details of sampling time relative to dose, time of last dose change and present daily dose schedule should always be stated on the assay request form to aid interpretation of the plasma concentration.

In clinical practice, total rather than free (active) drug concentrations are measured by conventional assay methodologies. Although, in most circumstances, these will correlate with free drug concentrations, this is not always the case:
In neonates, the frail elderly and in liver disease, plasma albumin may be reduced due to impaired production.

In renal dysfunction, particularly nephrotic syndrome, plasma albumin may be reduced due to loss into the urine.

In renal failure, accumulation of inhibitors of protein binding may further reduce binding, so the measurement of total concentration may underestimate free concentrations in all these conditions.

For some drugs (e.g. diphenylhydantoin and theophylline), saliva concentrations may reflect the free drug concentration more accurately and some laboratories can also measure free drug concentrations directly by ultrafiltration or equilibrium dialysis techniques.

AAG is an acute-phase protein that avidly binds many basic drugs (e.g. lidocaine, disopyramide, quinidine and verapamil). In situations where AAG may be raised, for instance after acute myocardial infarction, surgery, trauma or burns, or in rheumatoid arthritis and other inflammatory conditions, total drug concentrations may overestimate free drug concentrations. Conversely, AAG may be reduced in neonates, nephrotic syndrome and severe liver disease and the opposite holds true. Measurement of free drug concentration may thus be more helpful in such circumstances, although direct measurement of AAG concentration in plasma may allow the free concentration of some compounds to be calculated with reasonable accuracy (Routledge, 1986).

Surveillance and the prevention of adverse drug reactions

Many type B reactions occur in patients who are prescribed the same drug or a very similar agent to which they have had a previous adverse reaction. For this reason, the general practitioner and hospital medical records and the inpatient prescription sheets should all be clearly marked with a bright label so that the prescriber is aware of previous serious ADRs. Computerized systems have been developed to alert physicians to previous type B reactions to drugs and of appropriate drug administration rates, and their use has resulted in a reduced frequency of type B reactions (Classen et al., 1991; Evans et al., 1994). Unfortunately, these systems are not yet widely available, and the vigilance of healthcare professionals is still the most important factor in avoiding such episodes.

Drug interactions

Interactions between drugs have been observed for nearly 100 years and have been described under the classical headings of antagonism, synergism and potentiation. Many interactions have been, and still are, deliberately used with therapeutic benefit, but adverse interactions are becoming an increasingly important problem for several reasons:

- Newly introduced drugs are often much more potent than their predecessors and act on fundamental biochemical and enzymatic pathways or receptors.
Progress in therapeutics, together with an increasingly aging population, has resulted in increased polypharmacy.

Drug interactions have been estimated to account for 6–30 per cent of all ADRs (Orme et al., 1991). Since adverse reactions are relatively common and interactions involve many different types of drugs, it may appear at first sight an almost impossible task for any physician to retain a perspective on the subject. Fortunately, although more than 1000 drug interactions have been described, the number that are clinically important is much smaller and involves a relatively small number of pharmacological groups of drugs (Seymour and Routledge, 1998). It is also important to recognize that perhaps more than 50 per cent of drug interactions result in some loss of action of one or other of the drugs. These are more likely to be overlooked, since alternative explanations, such as poor compliance, may be considered as reasons for inefficacy of the treatment.

Mechanisms
Interactions may occur outside or inside the body:

- The former are referred to as pharmaceutical incompatibilities and they generally occur when two or more agents are mixed in infusions or in the same syringe, or when a drug reacts with the infusion fluid itself.

- Interactions occurring within the body result from either an alteration in the delivery of the drug to its site of action (pharmacokinetic interactions) or from a drug-induced alteration in receptor or organ response to another agent (pharmacodynamic interactions). Often, these characteristics are altered when other drugs are given.

Both pharmacokinetic and pharmacodynamic interactions are equally important. Pharmacokinetic interactions will be discussed first, because these must generally first be excluded before the possibility of a pharmacodynamic interaction is investigated.

Pharmacokinetic interactions
These may occur during any one or more of the pharmacokinetic processes whereby the drug reaches its site of action and is then eliminated (i.e. absorption, distribution, metabolism and excretion). Such interactions may result in either an increased or decreased drug concentration at the site of action. Although the former may result in drug toxicity, a decreased efficacy may put the patient at increased risk from the effects of the disease.

Absorption
For most drugs, absorption is a passive process that is dependent upon the properties of the drug and its particular formulation, the pH of the absorption medium and the length of time the drug remains at the site of absorption. Drugs may interact with each other during all these processes, as well as directly with each other by formation of poorly absorbed complexes. It is important to distinguish in this context between changes in the rate and extent of drug absorption:
• Alteration of the rate of absorption alone will change the shape of the concentration–time curve after oral administration, but it will not alter the average or steady-state drug concentration. Such changes may be important, however, in the case of drugs given in single doses and in which a threshold concentration for drug effect exists (e.g. analgesics). A delay in absorption under these circumstances, especially if the rate of elimination of the drug is high, may result in an inability to reach a drug concentration associated with drug efficacy.

• In contrast, a change in extent of absorption will result in a change in variation in delivery of drug to its site of action both after a single dose and repeated doses.

Drug-induced changes in the pH of the gastrointestinal media may increase or decrease the rate and extent of drug absorption. Alkalis may aid dissolution of poorly soluble acidic drugs (e.g. aspirin) and stimulate gastric emptying. Alterations in gut motility induced by one drug may alter the rate and/or extent of absorption of another. Sparingly soluble drugs (e.g. digoxin) may be unable to undergo complete disintegration and dissolution when gastric emptying and intestinal transit rates are increased by such drugs as metoclopramide and their extent of absorption may therefore be reduced. In contrast, since the greatest proportion of drug absorption occurs in the small intestine, the rate-limiting step for absorption of well-absorbed drugs is the rate of gastric emptying. Metoclopramide, therefore, increases the absorption rate of paracetamol by increasing the gastric emptying rate. The opposite effects are seen with anticholinergic and opiate drugs.

Certain agents may complex with drugs and reduce their absorption. Aluminium, calcium, or magnesium antacids may thus reduce the absorption of several drugs, including 4-quinolone antibiotics, tetracyclines and iron. Ion-exchange resins, such as cholestyramine and colestipol, have been shown to bind to, (and thereby to decrease the extent of absorption of) warfarin, thyroxine and triiodothyronine, and digitalis glycosides.

Drugs may also interfere with absorption of other drugs more indirectly by causing malabsorption syndromes. Colchicine, neomycin and para-amino salicylic acid (PAS) may impair the absorption of folate, iron and vitamin B<sub>12</sub> by this means. The causes of drug absorption interactions are therefore numerous. Their importance may have been underestimated, since physicians are more likely to attribute inadequate response to other factors, such as poor compliance with prescribed therapy.

**Drug distribution**

Most drugs do not merely distribute throughout body fluids, they are bound or in some cases actively transported into blood and tissue elements. Drugs that are relatively inefficiently cleared by the organ of elimination (e.g. liver or kidney) have been termed ‘restrictively eliminated’ compounds, since their clearance, either by glomerular filtration or by liver metabolism, is limited by their degree of binding in the blood. Restrictive elimination occurs when the extraction ratio of the drug is less than the free fraction of that drug in blood. Displacement of such compounds from plasma protein binding sites will cause an immediate rise in free drug concentration. This increase will only be temporary, however, since the increase in free fraction will allow more of the drug to be eliminated until a new steady state is reached when the unbound (free) concentration returns to its original level. Permanent changes will be seen in the total plasma concentration, since total clearance of the drug has
been increased. This will only be detected if total plasma concentration is measured (this is the moiety most often measured by laboratories), since the effect at steady state will be unchanged. The magnitude of the temporary increase of unbound drug will depend upon:

- the original volume of distribution of the displaced drug
- the original degree of binding in the blood
- the degree of binding to tissues.

Thus, it is likely plasma protein displacement interactions will cause (and then only temporarily) a significant increase in free drug concentration only when poorly cleared drugs have a high degree of binding in plasma and poor binding to tissues. Although warfarin fulfils these criteria, several drugs that have been shown to displace warfarin from plasma binding sites, such as phenylbutazone, also interact in more important ways with warfarin, e.g. competition for metabolism. Therefore, it is difficult to estimate what (if any) effect is produced by the transient increase in free-drug concentration.

Many drugs are effectively cleared by the body, so that the extraction ratio of the eliminating organ(s) is greater than (and therefore not limited by) the fraction of drug free in the blood. Displacement of these compounds from plasma binding sites will theoretically result in a permanent increase in free drug concentration, but only a temporary increase in total drug concentration in blood. The magnitude of the permanent increase in free drug concentration will also depend upon the relative degrees of initial binding in blood and tissues, being greatest for drugs with high binding in blood and poor tissue binding. To date, no clinically important interactions involving this mechanism alone have been described for highly cleared drugs.

**Elimination**

Drugs are either excreted directly in the urine or are first metabolized by other organs (e.g. the liver or gut) to more water-soluble products, which can be more easily excreted by the kidney. Interactions may occur during any of these processes and result in enhancement or diminution of drug effect.

**Hepatic metabolism**

The chemical reactions involved in drug metabolism are generally classified as either:

- phase 1 (oxidation, reduction or hydrolysis), or
- phase 2 (conjugation with glucuronic acid, sulphates or acetate).

Any drug may undergo one or more of these types of metabolism before being excreted by the kidney, but the most important of these are oxidation and glucuronic acid conjugation. Because of its size, enzyme content and plentiful blood supply, the liver is the major site of drug metabolism, although the intestine, lung and kidney have been shown to be other minor sites of metabolism.

The major group of drug-metabolizing enzymes, the cytochrome P450 system, is
extremely versatile and is responsible for the biotransformation of many drugs and endogenous compounds. Because of the relative nonspecificity of these pathways, several interactions can take place between drugs using this route of metabolism. Cytochrome P450 is now known to be made up of several subtypes or isozymes, and enzyme inhibition interactions have been reported with at least six of these (see Table 2.3). Some drugs are metabolized by several of these isozymes, either concurrently or sequentially. In addition, some drugs metabolized by these pathways can act competitively to inhibit metabolism of each other via that route. Other drugs (e.g. cimetidine or erythromycin) can inhibit more than one isozyme non-competitively, and so act on more than one pathway.

Drug clearance is a measure of the efficiency of removal of the compound and, unlike the elimination half-life $T_{1/2}$, is unaffected by drug distribution. For those drugs in which intrinsic clearance, and therefore efficiency of removal (extraction ratio), is high, systemic (intravenous) clearance is rate limited by blood flow to the organ. In contrast, the systemic clearance of poorly extracted compounds is limited predominantly by the intrinsic clearance ability of the organ. The lower the initial efficiency of removal, the more a given change in enzyme activity will alter systemic clearance. After oral administration, however, changes in intrinsic clearance will equally affect the clearance of drugs that are both poorly and well extracted by the liver. This occurs despite the fact that the systemic clearance of the oral dose of a highly extracted drug will be much less affected by any change in intrinsic clearance analogous to post-intravenous administration. The reason for this phenomenon is that increasing intrinsic clearance will increase the hepatic extraction ratio so that a much smaller proportion $F$ of the highly extracted drug will reach the systemic circulation, even for the first time. Thus, for all drugs that are completely absorbed from the gut and metabolized by the liver, the area under the plasma concentration–time curve (AUC) is independent of changes in blood flow.

Two important consequences emerge from these theoretical considerations:

- In contrast to poorly extracted drugs, changes in enzyme activity caused by other compounds will affect plasma levels of highly extracted drugs much more after oral administration than after the intravenous route. Poorly extracted drugs will be affected approximately equally, whatever the route of administration.

- Secondly, $T_{1/2}$ of orally administered highly extracted drugs will be much less affected by changes in intrinsic clearance than the half-life of poorly extracted compounds.

One example is the difference in lidocaine kinetics between patients with epilepsy receiving enzyme-inducing drugs and drug-free controls given oral and intravenous doses of lidocaine on separate occasions (Perrucca and Richens, 1979). The patients did not differ significantly from controls in $T_{1/2}$ after oral or intravenous administration or clearance after intravenous administration. Despite this, intrinsic (apparent oral) clearance (as measured by the AUC) was increased more than twofold in the subjects after oral administration. Thus, $T_{1/2}$ may be a poorer indicator of changes in hepatic drug metabolism than clearance or AUC, particularly for already highly efficiently cleared drugs (Routledge and Shand, 1981).

**Enzyme induction** Induction of the metabolism of one drug by another is an important mechanism for interactions. Several agents (e.g. phenobarbitone, diphenylhydantoin, primidone, carbamazepine and rifampicin) can increase the activity of many isozymes of
cytochrome P450. The delay between commencement of the inducing agent and the full effect (7–10 days) can make recognition of the interaction difficult. The offset of the interaction occurs over a similar period after the inducing agent is stopped, producing similar difficulties in identification.

Several agents have been implicated as inducers of hepatic drug metabolism. The more important ones are listed in Table 2.4. It is important to remember that not all patients receiving these agents will necessarily be affected since there is wide inter-individual variation.

The herbal medicine used for treatment of depression, St John’s Wort is derived from Hypericum perforatum, which is found widely across Europe. The extract contains many pharmacologically active constituents, some of which can induce microsomal oxidation down a variety of pathways, as well as the activity of the efflux pump, P-glycoprotein (Pgp), which will be discussed later. This results in increases in the clearance of several HIV protease inhibitors, HIV non-nucleoside reverse transcriptase inhibitors, ciclosporin, oral contraceptives (all metabolized via CYP3A4), some anticonvulsants, the S-enantiomer of warfarin (CYP2C9), and theophylline (CYP1A2).

Although interactions involving induction usually result in decreased drug action, toxicity may occur if toxic metabolite production is increased. Phenobarbitone increases the demethylation of pethidine to norpethidine, which may cause CNS depression and prolonged sedation in enzyme-induced subjects.

**Enzyme inhibition** Inhibition of drug metabolism is also a well-established and potentially more serious phenomenon, since it may lead directly to toxic concentrations of some drugs. As inhibition is, in many cases, competitive, two simultaneously administered drugs may inhibit the metabolism of each other. Several of the compounds observed to cause clinically significant inhibition of metabolism are listed in Table 2.5. One important interaction illustrating both inhibition and induction of drug metabolism is that between phenylbutazone and warfarin. Warfarin (like many other drugs) consists of a racemic mixture of equal parts of the dextro (R) and laevo (S) enantiomers (stereoisomer).
Phenylbutazone increases the clearance of R-warfarin and simultaneously decreases the clearance of S-warfarin. It does not, therefore, affect the clearance of warfarin when it is measured as the racemate. Since S-warfarin is approximately five times more potent as an anticoagulant than R-warfarin, however, the overall effect of the interaction is to increase the anticoagulation produced by the racemic drug.

Renal excretion

Drugs are excreted by the kidney both by glomerular filtration and tubular secretion. They may then be reabsorbed by active tubular reabsorption. Changes in any of these processes induced by one agent may result in altered excretion of another compound. Furosemide in low doses may reduce the renal clearance of cephaloridine and gentamicin, and this has been attributed to a furosemide-induced reduction in GFR. However, other work has indicated that furosemide may increase GFR; so, although furosemide may increase the nephrotoxicity of cephalosporins and the otoxicity of gentamicin, the role of altered GFR in these interactions is unclear. Tubular secretion is an active process by which some acids and bases are transported into tubular fluid against a concentration gradient. Competition for this relatively nonspecific process between two acidic or two basic drugs may lead to diminished excretion of one or both agents. Clinically significant interactions will only occur, however, if this process is responsible for a major proportion of the total excretion of the drug(s). Probenecid and salicylates can reduce the elimination of methotrexate by this mechanism and may lead to severe toxicity if methotrexate dosage is not adjusted accordingly. Weak bases are less ionized when the urine is alkalinated by other agents. Acetazolamide and antacids, which render urine alkaline, have thus caused toxicity due to impaired excretion of the basic compound, amphetamine, and also reduce quinidine excretion by the kidney. Conversely, alkalination of urine may increase the excretion of acidic drugs, such as salicylates and phenobarbitone, and this interaction has been put to clinical use in the treatment of poisoning by these agents with forced alkaline diuresis.

Table 2.5  Some clinically important inhibitors of drug metabolism

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<td>Amiodarone</td>
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<td>Cimetidine</td>
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<td>Some macrolides</td>
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<td>Monoamine oxidase inhibitors&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Metronidazole</td>
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<td>Some selective serotonin re-uptake inhibitors</td>
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<sup>a</sup> Relatively selective inhibitors of certain metabolic pathways.
Drug transport

It is becoming increasingly clear that the penetration of some drugs into cells and tissues, and the bioavailability and excretion of certain compounds by the liver and kidneys, is affected by a group of energy-dependent membrane transporters found in a variety of cells throughout the body. The best known of these is the ATP-dependent multidrug efflux transporter Pgp. It is a surface phosphoglycoprotein found in the gut, heart, kidney, liver, brain, testes, placenta and adrenal glands, where it pumps drugs out of the cell. It is coded for by the multidrug resistance locus, MDR-1, and substrates include a variety of compounds, particularly those metabolized via CYP3A4, with which it appears to share some homology. Substrates for Pgp include digoxin, quinidine, ciclosporin, some HIV protease inhibitors, and many agents used in cancer chemotherapy and some antihistamines. Pgp, by acting as an absorption barrier and excreting drugs into the intestinal lumen, can cause reduced bioavailability of certain compounds. It can also prevent accumulation of drugs into cells in the vascular compartment as well as the interstitial space. Finally, it has a role in enhancing excretion of xenobiotics via the urine and bile. Teleologically, it appears to be a defence mechanism to prevent uptake of certain substances into organs such as the brain (Ambudkar et al., 1999).

In addition, there are energy-dependent organic anion transporters (OATs), which mediate the hepatic uptake of organic anions, canalicular multispecific OATs which are probably involved in the gastrointestinal uptake of organic anions, OAT polypeptides (which mediate renal uptake of organic anions) and multidrug resistance proteins, responsible for the biliary excretion of organic anions (Kusuhara and Sugiyama, 2002). Some interactions (e.g. the inhibition of digoxin clearance by quinidine) may be caused in large part by competition for a transporter (Pgp in the case of quinidine and digoxin). Recently, a relational database with details of this rapidly changing field has become available (Yan and Sadee, 2000) at http://lab.digibench.net/transporter/.

Pharmacodynamic factors

Pharmacodynamic interactions occur when one drug alters the response of another by interaction at the receptor site or acts at a different site to enhance or diminish the first drug’s effects. The interactions that were first recognized were those in which drugs act at the same receptor site:

- Drugs that combine with the receptor to initiate a response are termed agonists.
- Drugs that interact with the receptor to inhibit the action of an agonist, but do not initiate a response themselves, are termed antagonists.

Antagonism may be competitive, when increasing the agonist concentration restores its effects completely, or it may be non-competitive (irreversible). Partial agonists act on the same receptor as the agonist to initiate a minor response, but by occupying a significant fraction of the receptors they antagonize the action of more potent agonists. Thus, naloxone is a potent antagonist of the agonist action of morphine. Nalorphine, however, although possessing antagonist activity, is also a partial agonist and may add to respiratory depression produced by morphine.
Many of the interactions at the receptor site are used to advantage clinically, either to antagonize or augment the effect of endogenous mediators or to counteract toxicity due to overdose of administered agents. Unwanted interactions most commonly occur when one fails to realize that a drug acting at one receptor may also act at another receptor. Antihistamines, which block H1 receptors, also have muscarinic anticholinergic activity, for example, as do some phenothiazines and tricyclic antidepressants; co-administration of two or more of these agents can lead to excessive anticholinergic activity.

Pharmacodynamic interactions may also occur when two drugs act at separate sites to cause potentiation, summation or antagonism of their normal actions. Such interactions are often used clinically in the treatment of:

- angina (e.g. beta blockers and vasodilators)
- hypertension (beta blockers and diuretics)
- malignant disease (combined cytotoxic chemotherapy).

However, these interactions may also occur inadvertently. Several drugs, including anabolic steroids, clofibrate, quinidine and salicylates, act on the synthesis of vitamin K-dependent clotting factors or the normal coagulation mechanism to potentiate the anticoagulant action of warfarin. Another long-recognized example is the ability of diuretic-induced hypokalaemia to potentiate digoxin toxicity. Even if the effects are only additive rather than synergistic, they may be sufficient to cause adverse effects in some cases.

Sometimes the effect may be more than additive. The estimated relative risk of peptic ulcer in elderly subjects receiving NSAIDs is around 4 (Griffin et al., 1991). The relative risk in comparable subjects receiving corticosteroids is only 1.1 (Piper et al., 1991). Patients taking both types of compound concomitantly have a risk for peptic ulcer disease 15 times greater than that of non-users of either drug (Piper et al., 1991).

Pharmacodynamic interactions that occur when drugs act at different sites may also result in a loss of drug efficacy. For example, the use of NSAIDs in patients receiving antihypertensive therapy with beta blockers, thiazides and angiotensin-converting enzyme (ACE) inhibitors can result in a loss of antihypertensive action, probably because NSAIDs promote sodium retention.

**Risk factors for drug–drug interactions**

It is well known that the potential for drug–drug interaction increases both with age and with the number of medications prescribed. As increasing numbers of effective strategies for primary and secondary prevention of disease are discovered, the number of agents that patients receive is also increasing (e.g. in ischaemic heart disease), so this issue will increase in importance in the future. It is clear that the more dependent patients in institutionalized settings (e.g. nursing homes or long-stay medical wards) have an increased risk of ADRs, including interactions. This may be explained partly by the fact that patients cared for in these establishments are more frail and ill and, therefore, receive many drugs. Thus, residents of nursing homes are often prescribed an average of five to eight regular medications. Increased frailty is an important risk factor for ADRs, even in outpatients, and excessive psychotropic medication, which may be used in such individuals, is a particular concern because of the risk of adverse reactions and interactions. A recent study showed that
the number of prescribing physicians was a determinant of the risk of potentially inappro-
priate drug combinations. The use of a single primary care physician, but particularly the
use of a single dispensing pharmacy, lowered this risk significantly (Tamblyn et al., 1996).

Detection and management

These issues are essentially the same as for ADRs in general. The physician should maintain
a high level of surveillance, particularly when drugs with a low therapeutic ratio are
prescribed to patients with a high risk for an adverse interaction. A recent study of patients
attending a cardiology outpatient service revealed 545 discrepancies in 239 patients (76 per
cent) between what doctors prescribed and what patients were taking. There was a
correlation between the discrepancies and the patients’ age and number of recorded
medications. Over-the-counter or herbal therapies were involved in one-third of the
discrepancies (Bedell et al., 2000), so that a careful history of all agents taken should be
elicited. Some adverse drug events, including ADRs, can be detected using computerized
decision-support systems (Hunt, 1998; Wiffen et al., 2002), and their use in the clinical
situation should be encouraged.

Prevention

Guides to intravenous admixture incompatibility exist, but the possibility of their occurrence
can be minimized by taking the following precautions:

- Never add a drug to an infusion fluid unless absolutely necessary.
- Never add more than one drug to the syringe or infusion fluid.
- Do not add drugs to whole blood or blood products, amino acid or lipid solutions,
mannitol or sodium bicarbonate.

An inordinate proportion of serious adverse interactions occur with relatively few
therapeutic agents. These are generally drugs in which the therapeutic ratio is small, such as
oral anticoagulants, cytotoxic drugs, anticonvulsants, and hypotensive and hypoglycaemic
agents. The decision to use these agents should be considered carefully and the patient
monitored closely.

Drugs may be prescribed for many years without any assessment of their continuing
therapeutic role. The list of drugs a patient receives should, therefore, be regularly reviewed.
On some occasions it may be appropriate to withdraw one or more drugs and subsequently
monitor the patient. For example, in the elderly it may be possible to consider stopping:

- NSAIDs in osteoarthritis
- digoxin in individuals in sinus rhythm
- diuretics for idiopathic oedema
- neuroleptics, such as prochlorperazine, prescribed for nausea or ‘dizzy turns’.

Great care is recommended in those situations where patients have been on drugs that can
produce dependence (e.g. long-term benzodiazepines or barbiturates), since sudden withdrawal can result in a severe withdrawal syndrome. Similarly, gradual withdrawal may be necessary for many agents (e.g. nitrates or beta blockers used in angina or anticonvulsants used in epilepsy) to avoid rebound, with worsening of the condition. Nevertheless, a shorter drug list is an important factor in reducing the risk of interactions.

Drug–drug interactions may not be immediately obvious when combinations are first prescribed, so patients should be encouraged to form a ‘prescribing partnership’, alerting doctors and other prescribers to symptoms that occur when new drugs are introduced. Nonspecific complaints, such as confusion, lethargy, weakness, dizzy turns, incontinence, depression and falling, should all prompt a closer look at the patient’s drug list. The patient should be warned of the dangers of taking new medications (particularly over-the-counter remedies) without obtaining advice concerning potential interactions. The fewer people prescribing for the patient, the lower the risk that an interaction will occur iatrogenically (Tamblyn et al., 1996).

On a broader front, more sensitive and reliable parameters of drug effect are needed. It is reassuring to note that when physicians have a reliable and simple measure of drug effect (e.g. for anticoagulants with the one-stage prothrombin time or INR) drug interactions are often quickly recognized and therapy can be adjusted appropriately.

**Pharmacogenetics and the prevention of adverse drug reactions**

As our understanding of pharmacogenetic (and environmental) influences on inter-individual differences in pharmacokinetics and pharmacodynamics increases, bespoke prescribing (choosing the right dose of the right drug for the right patient) will hopefully be increasingly possible. Indeed, *Pharmacogenomics* has been defined as ‘The science of increasing the effectiveness of drugs and minimizing their side effects by matching drugs to people according to their genetic make up’.

Pharmacogenomics shows great promise in relation to drug safety (McLeod and Evans, 2001). However, phenotyping individuals for certain polymorphisms of drug metabolism or response can be time consuming and often requires administration of exogenous agents (Hutchings and Routledge, 1986). Even when specific phenotyping tests can be performed directly on blood samples, the uptake is variable (Holme et al., 2002). Genotyping may also be time consuming and expensive, and not all relevant alleles may yet have been identified for some important polymorphisms. For these reasons, genotyping is not yet used routinely in clinical practice, and prescribers tend to avoid using drugs in which genetic polymorphism may result in potential toxicity for a small proportion of their patients. Increased availability of pharmacogenetic testing may help us to identify those at risk of toxicity to specific agents and avoid specific medicines in at-risk groups (Ozdemir et al., 2001).

When testing is available for a range of polymorphisms, personal pharmacogenetic profiling may then become a possibility in the clinical setting. Pharmacogenetically based prescribing guidelines could then be developed, and the pharmaceutical industry can then concentrate its efforts on developing new drugs based on specific genotypes (‘drug stratification’; Roses 2000, 2002a, b; Wolf et al., 2000). For example, screening using probe drugs and inhibitory monoclonal antibodies to identify the major contributory CYP450s (including those showing genetic polymorphisms) responsible for the metabolism of potential new chemical entities is already being used in early drug discovery (Donato and Castell, 2003; Soars et al., 2003).
Conclusions

Adverse drug reactions, of which drug–drug interactions are a special category, are a significant cause of morbidity and occasionally cause fatality. The risk of serious ADRs is highest for only a few drug groups (e.g. cytotoxics, hypotensives, NSAIDs, hypoglycaemics and oral anticoagulants) and in certain groups (e.g. the frail elderly and those with renal or liver disease or heart failure). Adverse drug reactions may be difficult to detect because they can mimic other diseases and may have very few specific features. In addition, there are often few specific or sensitive \textit{in vitro} tests, and rechallenge to the agent may be precluded because of a possible severe response. The diagnosis of ADRs may, therefore, have to rely on circumstantial evidence, based on the time course of onset relative to the introduction of the drug or change in dose and the response to dose withdrawal or drug discontinuation.

Fortunately, many ADRs and adverse drug interactions can be avoided with a knowledge of basic pharmacological principles and judicious choice of drugs and doses. When an ADR is suspected, a report to the regulatory authority and company will help identify risks and inform decisions about risk–benefit, and thus help to protect others from similar problems in the future. Although the use of pharmacogenetic testing may help us to avoid toxicity in at-risk groups, as things stand at present, our limited understanding of type A and type B toxicity and the changing environmental influences determining risk of ADRs means that vigilance will continue to be a vital part of drug safety. Because medicines can only ever have a ‘provisional licence’ for drug safety, careful surveillance safety should continue during the drug development process and throughout the life span of the drug as a therapeutic agent (Rawlins, 1995). Complacency in this respect can end in disaster (Routledge, 1998).

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