CHAPTER 5

Drugs as toxic substances

'There are no safe drugs, only safe ways of using them.'
'Doctors put drugs of which they know little, into our bodies of which they know less, to cure diseases of which they know nothing at all'.
Voltaire

Chapter outline

This chapter will use examples to illustrate the types of drug toxicity:

- Types of drug toxicity
- Paracetamol
- Aspirin
- Hydralazine
- Halothane
- Debrisoquine
- Thalidomide
- Drug interactions
- Altered responsiveness – glucose 6 phosphate dehydrogenase deficiency

Introduction

Most human beings and indeed many other animals are exposed to drugs sooner or later in their lives. However, drugs are substances *designed* to have biological activity and although the layman expects them to be perfectly safe it is not surprising that toxic effects do sometimes occur especially when drugs are wrongly used. However, drugs have made and will continue to make a major contribution to human health and we must accept a measure of risk attached to these benefits.

The tragedy which first made the public and probably also the medical profession fully aware of this unpleasant fact was that caused by the drug **thalidomide**. This event, perhaps more than any other, proved to be a major watershed for awareness of drug toxicity and the need for

better legislation and testing of pharmaceuticals. Consequently, we will consider this as one of our examples which will also serve to illustrate the problem of teratogenesis.

There are several different types of drug toxicity: **adverse effects** or **side effects** occurring during proper therapeutic usage; acute toxicity due to **overdosage**; **idiosyncratic reactions** which occur during proper therapeutic usage but rarely; **interactions** with other drugs or other substances being taken concurrently which lead to toxic effects; and **habitual abuse** of drugs leading to chronic toxicity. Drug overdoses come within the bounds of clinical toxicology as does accidental ingestion of hazardous substances whereas abuse of drugs including their use for murder is the domain of the forensic toxicologist.

The basic mechanisms underlying these types of toxicity may also be summarized:

1 direct and **predictable** toxic effects due to altered or inhibited metabolism and occurring after **overdoses**;

2 toxic effects occurring after repeated **therapeutic doses** with a metabolic, pharmacological or maybe immunological basis;

3 direct but **unpredictable toxic effects** occurring after single therapeutic doses and due to idiosyncratic metabolism or a pharmacodynamic response;

4 toxic effects due to **another drug or substance** interfering with the disposition or pharmacological response of the drug in question.

Examples of some of these types of drug toxicity will be considered in this chapter.

Paracetamol

Overdosage with drugs is now one of the commonest means of committing suicide and one of the drugs most commonly involved in the UK is paracetamol with at least 200 deaths a year being due to overdoses of this drug. As well as intentional, *suicidal* overdoses, *accidental* poisoning has also occurred and recently been highlighted. This occurred as a result of patients and doctors being unaware that some proprietary preparations contain paracetamol. Thus, repeated **self medication** with paracetamol tablets possibly along with cold cures which may also contain the drug has lead to fatal overdosage in at least one case (see *Pharmaceutical Journal,* Bibliography). Paracetamol is a minor **analgesic** which is very safe provided only the normal therapeutic dose of one or two tablets (500 mg) is taken. However, after overdoses, where fifteen or twenty tablets may be taken, **fatal liver damage** can result. Fortunately an understanding of the mechanism underlying paracetamol toxicity has led to a method of *antidotal treatment* which is now able to prevent the fatal outcome in many cases.

Paracetamol is metabolized mainly by **conjugation** with sulphate and glucuronic acid. Only a minor proportion is metabolized by **oxidation** which is catalyzed by the microsomal mono-oxygenases (Figure 5.1). This produces a metabolite which is toxic but is normally detoxified by reaction with **glutathione** (see Chapter 3). However, research in experimental animals has shown that after an overdose several changes take place in this metabolic scheme. The pathways of conjugation are saturated and cofactors, especially sulphate, are depleted. As a result *more* paracetamol is metabolized by the oxidative pathway giving rise to the toxic metabolite. Sufficient of this metabolite is produced in the liver to deplete all the glutathione available. Therefore, the toxic metabo-

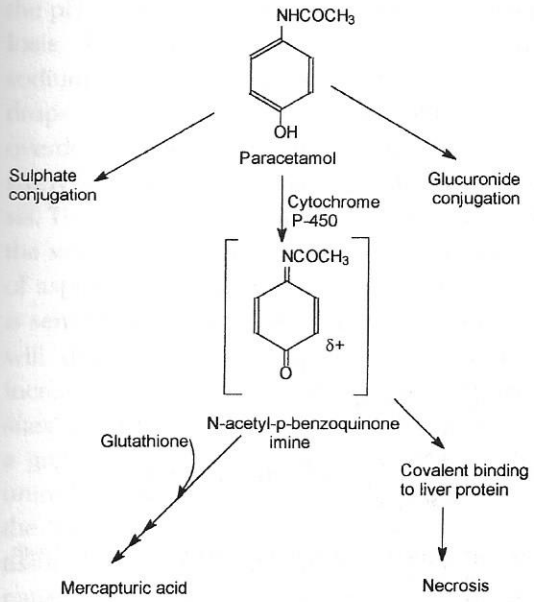

FIGURE 5.1 *The metabolism of the analgesic drug paracetamol.*
From Timbrell, J. A., Principles of Biochemical Toxicology, *Taylor & Francis, London, 2000.*

lite reacts with liver proteins instead of the glutathione and this causes direct tissue damage leading to **hepatic necrosis**.

Another factor of importance in relation to the susceptibility to toxicity is individual variation in metabolism, possibly as a result of the intake of other drugs. For example, excessive **alcohol** intake prior to paracetamol overdose may *increase* the liver damage as a result of induction of the particular isoenzyme of **cytochrome P450** involved in the metabolic activation of paracetamol. The elucidation of this mechanism suggested a means of treatment with an **antidote** to either regenerate glutathione or replace it with an alternative. The currently accepted treatment uses **N-acetylcysteine** given either orally or intravenously. Provided this is given within 10–12 hours of the overdose fatal liver damage is usually avoided.

A number of other drugs are taken in overdose for purposes of suicide and these cause various toxic effects. Such drugs include **aspirin**, **tranquillizers**, **barbiturates** and **opiates** but antidotes are not available for most of these. Supportive measures, decreasing absorption, increasing elimination or altering the distribution of the drug are the major types of treatment.

Aspirin (salicylate)

Acetylsalicylic acid, commonly known as aspirin, is still one of the most widely used minor analgesics and other salicylates also are used therapeutically. This drug is still an important cause of human poisoning resulting both from overdoses and from therapeutic use. These result in a significant number of deaths each year in the UK and other countries. In children the majority of deaths are from therapeutic overdose. The toxic effects are very much biochemical and physiological, with no clear target organ. However, aspirin poisoning illustrates how chemicals can cause toxicity or even lethality without damaging a particular tissue or organ specifically.

When used repeatedly, aspirin at therapeutic doses may accumulate in the patient and eventually reach concentrations that are toxic. The reason for this is that parts of the metabolism and hence elimination of aspirin are **saturable**. The majority of a dose of aspirin (acetylsalicylic acid) is hydrolysed by esterases to salicylic acid (Figure 5.2). Salicylic acid is then metabolized by conjugation with glucuronic acid or glycine. However, these conjugation steps are saturable and therefore elimination is reduced as the dose increases (Table 5.1). As can be seen from the table, the half-life of aspirin increases significantly even with only a small increase in the number of tablets. This means that a knowledge of the

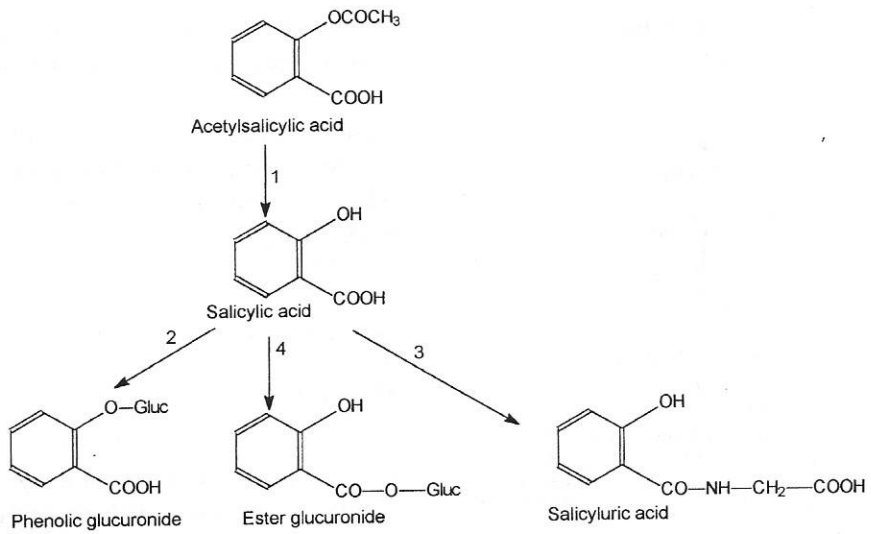

FIGURE 5.2 *The metabolism of aspirin. Step 1 (hydrolysis) yields the major metabolite salicylic acid which is conjugated with glucuronic acid (2 and 4) or glycine (3). Pathways 2, 3, and 4 are saturable.*
From Timbrell, J. A., Principles of Biochemical Toxicology, *Taylor & Francis, 2000.*

blood level of salicylate is very important for the clinical toxicologist.

The primary toxic effect of salicylate is that it interferes with the function of the electron transport chain in the mitochondria, leading to **uncoupling of ATP** production. This leads to a decrease in the production of ATP, increased utilization of oxygen and increased production of carbon dioxide.

This causes the patient to hyperventilate and salicylate also directly influences the control of breathing. These effects result in an increase in

TABLE 5.1 *The effect of dose on the disposition of aspirin and its toxicity*

No. of tablets (dose)	$T_{\frac{1}{2}}$ (h)	V_D L kg^{-1}	Blood level (μg ml^{-1})	Symptoms of toxicity
1 (300 mg)	3	0.1	43	None
2 (600 mg)	4	0.15	57	None
3 (900 mg)	5	0.17	76	None
12 (3.6 g)	6	0.2	25	Tinnitus
30 (9 g)	20	0.25	51.4	Hyperventilation, respiratory alkalosis, metabolic acidosis, fever
70 (21 g)	>20	0.30	1000	Coma, convulsions, respiratory failure, renal failure
100 (30 g)	>20	0.33	1299	Death

$T_{\frac{1}{2}}$: plasma half-life. V_D: volume of distribution.
Data from M. J. Ellenhorn and D. G. Barceloux, *Medical Toxicology*, 1988, Elsevier Science Publishing.

the pH of the blood known as **respiratory alkalosis**. The body corrects this by eliminating sodium bicarbonate into the urine and the pH drops. However, in children and after severe overdoses in adults, the pH may fall too extensively and the patient enters **metabolic acidosis**. This results in a change in the distribution of the salicylate. As salicylate, the main metabolite of aspirin, is an acid, elimination into the urine is sensitive to pH and when this falls, excretion will decrease as reabsorption in the kidney increases. Furthermore, distribution into the tissues, and particularly the brain, will increase as a greater proportion of the salicylate is in the unionized form. This will increase the effect of the salicylate on mitochondrial respiration in tissues and particularly the brain. Overall the patient suffers lack of ATP in crucial organs such as brain and heart, the temperature rises because the energy not used in the production of ATP is dissipated as heat. The excretion of bicarbonate that occurs in response to the rise in blood pH results in loss of sodium and water and the rise in temperature causes sweating. Consequently, the patient becomes dehydrated. As the urine pH has decreased, the salicylate and its metabolites are not readily excreted and the drug is not eliminated, which worsens the situation. Salicylate also has other effects such as inhibition of parts of Krebs' cycle and increased glycolysis (to produce the missing ATP) which causes further acidosis.

The toxicity is therefore due to the biochemical effects of low levels of ATP and acidosis. Treatment is relatively straightforward and involves reducing the acidosis by increasing the blood pH, giving a source of energy (glucose) and increasing the elimination of salicylate. These are all achieved by infusing **bicarbonate** solution containing glucose. The bicarbonate increases the pH of the blood, causing salicylate to dissociate and diffuse out of tissues such as the brain. It also increases the pH of the urine and this facilitates the excretion of salicylate into the urine and therefore elimination from the body. (See Figure 5.3.) This occurs because the pH of the urine becomes more alkaline and therefore the salicylate in

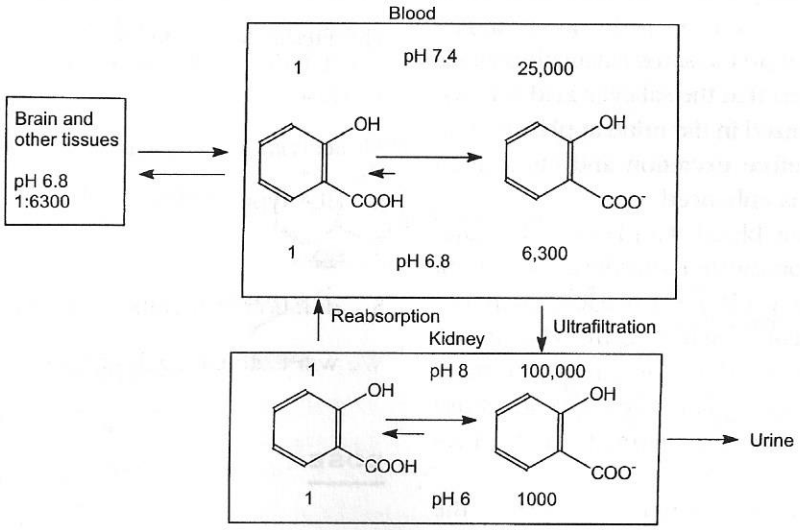

FIGURE 5.3 *The effect of pH on the dissociation, distribution and excretion of salicylic acid. The numbers represent the proportions of ionized and non-ionized salicylic acid.*
From Timbrell, J. A., Principles of Biochemical Toxicology, *Taylor & Francis, 2000.*

the ultrafiltrate produced by the kidney is more highly ionized. Consequently, less is reabsorbed back into the bloodstream. Knowing the pK_a of salicylic acid it is possible to calculate that if the urine pH is shifted from 6 to 8 there is a one hundred fold increase in the ionization of the acid. This is calculated as follows:

Using the **Henderson Hasselbach** equation (see Chapter 2, page 22).

$$pH = pK_a + \text{Log}\frac{[\text{salicylic acid}^-]}{[\text{salicylic acid}]}$$

The pK_a of salicylic acid is 3; therefore at pH 6 the ratio of ionized to non-ionized salicylic acid is:

$$6 = 3 + \text{Log}\frac{[\text{salicylic acid}^-]}{[\text{salicylic acid}]}$$

$$\text{Therefore } \frac{[\text{salicylic acid}^-]}{[\text{salicylic acid}]} = \text{anti-log } 6-3$$

anti-log 3 = 1000. Therefore there is 1000× more ionized salicylic acid than non-ionized at pH 6.

At pH 8 therefore the same calculation yields 100 000. It is clear that the salicylic acid is much more highly ionized in the urine at pH 8 than at pH 6 and therefore excretion and elimination from the body is enhanced.

Similarly in the blood at a pH of 7.4 the ratio of ionized to non-ionized salicylic acid is about 25 000 whereas at pH 6.8 it is 6300. Therefore when the patient is suffering from metabolic acidosis with a blood pH of maybe 6.8, there is more non-ionized salicylic acid able to diffuse into the tissues than at the normal blood pH 7.4 (see Figure 5.3).

The technique of changing the pH of the urine and blood in order to facilitate elimination of a chemical is also used to treat other cases of poisoning such as from barbiturates.

Hydralazine

The second example is of a drug toxicity which follows *normal therapeutic dosage* leading to adverse effects in a significant number of patients. This example is of particular interest because it illustrates the importance of the combination of several **factors** in the development of and susceptibility to an adverse drug effect.

The drug in question is the antihypertensive drug hydralazine. This drug causes a syndrome known as **lupus erythematosus** which has some similarities with rheumatoid arthritis. When the drug was first introduced in the 1950s, relatively high doses were used and the incidence of the adverse effect was high, occurring in over 10 per cent of patients. The use of the drug declined. However, use of lower doses in combination therapy reduced the incidence of the adverse effect although a recent report estimates that the true incidence is still unacceptably high with an overall value of 6.7 per cent. Recent studies have revealed that there are several factors which predispose patients to this particular adverse effect.

The factors so far defined are:

1 dose

2 acetylator phenotype

3 HLA type

4 sex

5 duration of therapy.

We will examine each in turn.

DOSE

This has already been mentioned. The incidence of the adverse effect seemed to be more common when doses of around 800 mg

daily were used compared with doses of less than 200 mg daily, which are more commonly used now. One recent study showed more clearly that the *incidence* was *dose related*; as no cases were reported at doses of 50 mg daily, there was a 5.4 per cent incidence after 100 mg daily and a 10.4 per cent incidence with 200 mg daily.

ACETYLATOR PHENOTYPE

Hydralazine is metabolized by the **acetylation route** which is a phase 2 metabolic transformation for foreign compounds which have an amine, sulphonamide or hydrazine group (see Chapter 3). This acetylation reaction is under *genetic control* in man and human populations can be divided into individuals of the rapid or slow **acetylator phenotype**. With hydralazine the adverse effect occurs almost exclusively in slow acetylators. As hydralazine undergoes acetylation it is probable that these differences in metabolism of the drug are responsible for the development of the syndrome. It may be that there is more of the parent drug available in slow acetylators which may initiate an immunological reaction. Alternatively, another pathway of metabolism may become more important in the slow acetylators (Figure 5.4). There is some evidence for this with the oxidative pathway, catalyzed by the **mono-oxygenases** being the most likely route. However there is now evidence that other enzymes, notably **peroxidases** such as those found in leucocytes are also able to activate hydralazine to yield the same metabolites (phthalazine and phthalazinone). However, which, if any, metabolite is responsible for the adverse effect is currently unknown.

HLA TYPE

It was found that the patients who suffered the syndrome were more likely to have the HLA type (tissue type) DR4 than those not affected. That is, the incidence of **HLA DR4** is 60 per cent in those patients with hydralazine-induced lupus compared to an incidence of DR4 in the normal population of 27 per cent. The role, if any of the HLA type in the development of the syndrome is currently unknown; it may simply be a marker which has an association with a gene involved in the predisposition for the disease.

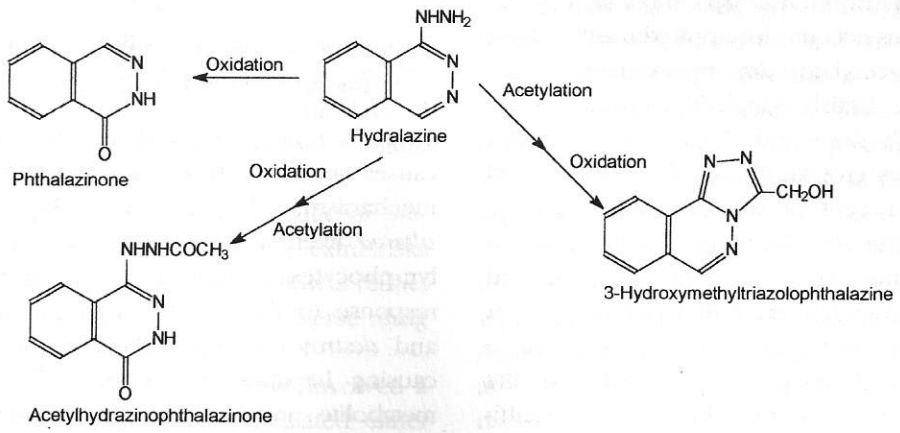

FIGURE 5.4 *The metabolism of the antihypertensive drug hydralazine.*
From Timbrell, J. A., Principles of Biochemical Toxicology, *Taylor & Francis, London, 2000.*

SEX

The adverse effect occurs *more commonly in women* than in men with a sex ratio of about 2:1 overall. However, one recent report quoted an incidence of 19.4 per cent in women taking 200 mg daily compared with an incidence in men of 4.9 per cent when measured three years after starting therapy. Currently there is no explanation for this sex difference as there is no evidence for any difference in acetylator phenotype or HLA type distribution between males and females nor for any difference in metabolism between males and females.

DURATION OF TREATMENT

The final factor is the duration of treatment with the drug; it seems to require an average of **18 months'** treatment for the development of the syndrome.

In view of these factors, the hydralazine-induced lupus syndrome is a particularly interesting example of an adverse drug reaction. The recognition of the predisposing factors allows an estimation of the likely incidence: the HLA type DR4 occurs in around 27 per cent of the population; females account for approximately 50 per cent; slow acetylators are approximately 50 per cent of the British population. Given a sufficiently high dose and duration of treatment these factors give an expected incidence of at least 7 per cent of the normal population. Although true incidence figures are hard to come by, the overall incidence in males and females as recently published is about 10 per cent. Alternatively, it can be regarded thus: a female, slow acetylator with the HLA type DR4 is *very likely to suffer the adverse effect* if a sufficient dose of the drug is given. This means that the adverse effect could be easily avoided if the prospective patients were screened for HLA type and acetylator phenotype.

The mechanism of hydralazine toxicity is currently unknown although it clearly has features characteristic of an allergic type of reaction. In fact, the adverse effect is usually manifested as a **Type III immune reaction** (see above, Figure 4.2).

Halothane

An example of an adverse drug effect which is a **very rare, idiosyncratic, reaction** is afforded by the widely used anaesthetic halothane. This may cause serious **liver damage** in between 1 in 10 000 and 1 in 100 000 patients. A mild liver dysfunction is more commonly seen but this probably involves a different mechanism.

The predisposing factors so far recognized in halothane hepatotoxicity are:

1 **multiple exposures**, which seem to sensitize the patient to future exposures;

2 sex, **females** being **more commonly affected** than males in the ratio 1.8:1;

3 **obesity**, 68 per cent of patients in one study were obese;

4 **allergy**, a previous history of allergy was found in one third of patients.

There is now good evidence that halothane causes hepatic damage via an **immunological mechanism**. The antibodies bind to the *altered* liver cell membrane and then **killer lymphocytes** attach to the **antibodies**. In response to this the killer lymphocytes lyze and *destroy* the liver cells of the patient, so causing hepatitis (Figure 5.5). The reactive metabolite involved in the immunological reaction is believed to be **trifluoroacetylchloride** which acylates proteins. This takes place

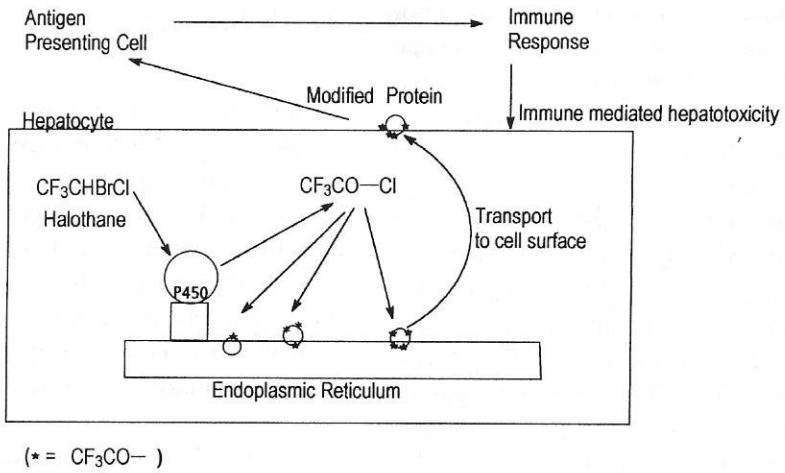

FIGURE 5.5 *The hypothetical mechanism of hepatotoxicity of the anaesthetic drug halothane. Halothane is metabolized by cytochrome P450 (P450) to a reactive metabolite (CF_3COCl) the trifluoroacetyl part of which binds covalently to proteins in the endoplasmic reticulum (*). The metabolite-protein conjugates are antigenic and elicit immune responses in susceptible patients.*
Adapted from Kenna, J. G. and Van Pelt, F. N. A. M. (1994) Anaesth. Pharmacol. Rev. **2**, *29.*

in the vicinity of the endoplasmic reticulum and consequently enzymes such as cytochrome P450 are believed to be acylated and become antigenic. Such antigens have been identified in liver.

The more common mild liver dysfunction is thought to be due to a direct toxic action of one of the halothane metabolites on the liver. The exact nature of the toxic metabolite is currently unclear although there is some evidence that the metabolite involved in the direct toxicity could either be a product of reductive or oxidative metabolism (Figure 3.10).

As with hydralazine the knowledge of predisposing factors, in this case the extra risks after multiple exposures, should allow a reduction in the incidence of this adverse drug effect.

The examples used so far have involved a direct toxic effect on tissues mediated either directly or via an immunological mechanism and leading to pathological lesions. The next example illustrates a type of adverse drug reaction in which a pharmacological effect is involved again with a genetic factor.

Debrisoquine

Debrisoquine is a little used **antihypertensive drug** which was found to show marked inter-individual variation. After the normal recommended therapeutic dose is given this drug may cause an *exaggerated* pharmacological effect, namely an *excessive* fall in blood pressure in a few individuals who have a particular genetic predisposition. It has been discovered that about 5-10 per cent of the white population of Europe and North America have this **genetic predisposition** and are known as **poor metabolizers** of debrisoquine. This is due to a *defect* in the mono-oxygenase system which catalyzes the hydroxylation of debrisoquine at the 4 position, the

major metabolic reaction (Figure 5.6). Poor metabolizers have almost complete absence of the cytochrome P450 isozyme which catalyzes the hydroxylation of debrisoquine.

As this metabolic reaction is the *major* route for removal of the drug from the body, such patients have *higher* plasma levels of the unchanged drug after a normal therapeutic dose than normal subjects. As debrisoquine itself is responsible for the hypotensive effect the result is an excessive fall in blood pressure (Figure 5.7). This is another example of unexpected toxicity occurring in a small proportion of the patients exposed. In this case, however, the metabolic mechanism seems fairly clear.

A similar example is the genetically determined toxicity of **succinylcholine**. This again results from reduced metabolism in certain individuals due to an **enzyme variant**. Succinylcholine is a **muscle relaxant** which normally is rapidly removed by metabolic hydrolysis and its duration of action is correspondingly short. In individuals with a *defect* in the **cholinesterase** enzyme responsible for the hydrolysis, however, metabolism is slow and consequently relaxation of muscle is *excessive* and *prolonged*.

Thalidomide

Thalidomide became notorious as the drug which caused **limb deformities** in children born to women who had used the drug during pregnancy. The drug is now a well established **human teratogen**. The thalidomide disaster is particularly important as it was the *watershed* for drug safety evaluation because it was perhaps the first *major* example of drug-induced toxicity. Thalidomide is a **sedative drug**, which was sometimes used for the treatment of morning sickness, and which seemed to be relatively non-toxic. However, it eventually became apparent that its use by pregnant women was associated with a very rare and characteristic limb deformity known as **phocomelia** in which the arms and legs of the infant were foreshortened. It became clear that these deformities were associated with the use of thalidomide on **days 24–29 of pregnancy**. The malformations were initially not reproducible in rats or rabbits and had not been detected in the limited toxicity studies carried out by the company manufacturing the drug. The mechanism underlying the effect is still not understood. Thalidomide is an *unstable*

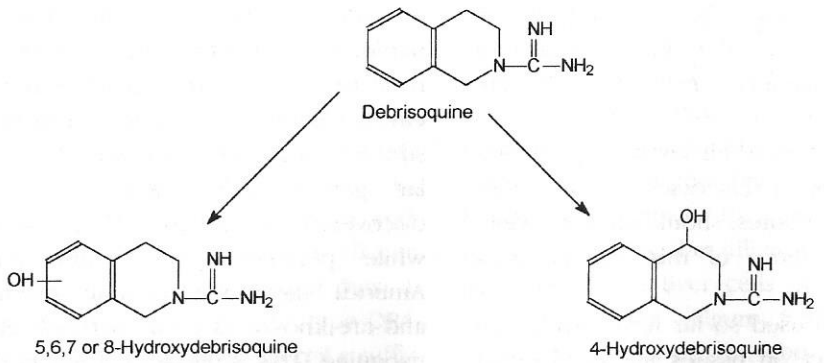

FIGURE 5.6 *The metabolism of the antihypertensive drug debrisoquine.*
From Timbrell, J. A., Principles of Biochemical Toxicology, *Taylor & Francis, London, 2000.*

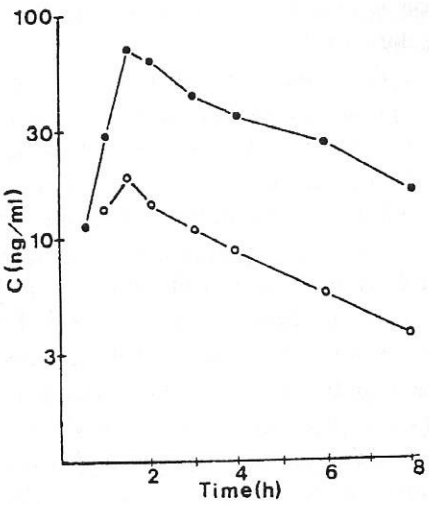

FIGURE 5.7 *The plasma concentration (C) of debrisoquine after a single oral dose (10 mg) in human subjects of the extensive (○) and poor (●) metabolizer phenotypes.*
Data from Sloan et al. *(1983)* British Journal of Clinical Pharmacology, **15**, *443*.

molecule and gives rise to a number of **polar metabolites** which are derivatives of glutamine and glutamic acid but the ultimate toxic metabolite has not yet been identified. Interestingly one of the isomers of thalidomide (the **S-enantiomer**) is more embryotoxic than the other. This is an illustration of the importance of **chirality** as a chemical factor affecting toxicity which has only relatively recently been recognized.

Thalidomide is an exceptionally *potent* teratogen, but because it has very low maternal toxicity in humans and low toxicity to experimental animals it was allowed to be marketed and used as a drug by pregnant women. It was detected as the cause of the deformities from **epidemiological data**, when an astute physician associated the exceedingly unusual effects with use of the drug.

There are many other examples of adverse drug reactions which can be found in the literature and the interested reader should consult the references given in the bibliography at the end of this chapter.

Drug interactions

The problem of interactions between drugs is a major one, particularly with the growth in polypharmacy and **multiple drug prescribing**. Although the physician and the pharmacist should be aware of such interactions new and unexpected interactions can and do appear. Interactions may be due to any one of a number of mechanisms, such as **interference** in the **metabolism** of one drug by another, interference in the **disposition** of one drug by another or alteration of the **pharmacological response** to one drug by another.

Many drugs may interfere with the metabolism of another drug either by **inducing** or **inhibiting** the enzymes involved (see Chapter 2). The best known example is that of barbiturates, such as **phenobarbital**, which induce the mono-oxygenase enzymes and so, by *altering* the *rate* or *route* of metabolism of other drugs, may *alter* their **toxicity**. Paracetamol overdoses are *more severe* if such inducing drugs have been taken, because metabolism via the toxic pathway catalyzed by the microsomal mono-oxygenases is enhanced (see above). Enzyme induction may also *decrease* the pharmacological or toxicological effects of a compound. For example, use of the antitubercular drug **rifampicin**, which is also a microsomal enzyme inducer, increases the metabolism of **contraceptive steroids** and so reduces their efficacy, sometimes resulting in unwanted pregnancies. Whether the toxicity of a particular drug will be increased or decreased will depend on the particular drugs involved and the mechanism of the toxic effect.

Interference in the disposition of one drug by another is a common interaction, particularly involving *displacement* of a drug from a binding site, typically from binding to **plasma proteins**. A well-known example of this is the displacement of the anticoagulant **warfarin** from plasma protein binding sites by **phenylbutazone**, an anti-inflammatory drug. This results in an elevated plasma level of warfarin leading to excessive anticoagulant activity and haemorrhage.

Altered responsiveness: glucose-6-phosphate dehydrogenase deficiency

Occasionally drug toxicity may occur in some individuals due to an unusual sensitivity, i.e. idiosyncrasy. Perhaps the best known example of this is the acute, drug-induced **haemolytic anaemia** due to a *deficiency* in the enzyme glucose-6-phosphate dehydrogenase. This enzyme, which has a major role in intermediary metabolism in the **pentose phosphate pathway**, is important in maintaining the **NADPH** concentration in the red blood cell. NADPH is necessary for maintaining the level of reduced **glutathione** in the red cell, which in turn protects the red cell from oxidizing substances such as the metabolites of certain drugs:

$$GSSG + NADPH + H^+ \rightarrow 2GSH + NADP^+$$

$$\text{Glucose-6-phosphate} + NADP^+ \xrightarrow{G6PD} \text{6-phosphogluconate} + NADPH$$

Patients who have this particular genetic defect suffer acute haemolytic anaemia when they take drugs such as the antimalarial **primaquine** or are exposed to certain types of foreign compounds such as **aniline** derivatives. **Fava beans** contain a substance which will precipitate haemolytic anaemia in susceptible individuals, hence the term favism.

The deficiency in glucose-6-phosphate dehydrogenase activity is the result of variants in the enzyme rather than complete absence. The enzyme variants are intrinsic to the red blood cell and so red blood cells from victims will be responsive *in vitro*. On challenge with a suitable drug these red blood cells will lyze and it can be shown that the level of glutathione is *lower* than in non-sufferers and in fact the glutathione level shows a bimodal distribution. It is a **genetic defect** carried on the **X chromosome**, so it is **sex-linked** but the inheritance is not simple. Overall **5–10 per cent** of **Negro males** suffer the deficiency and will suffer acute haemolytic anaemia if challenged with drugs such as primaquine. The highest incidence (53 per cent) is found in male Sephardic Jews from Kurdistan. There are many compounds which will cause haemolytic anaemia in susceptible individuals, some of which require metabolism to reactive metabolites, others not.

Abuse of drugs, alcohol and certain volatile solvents is becoming increasingly common in modern society and consequently so also is toxicity due to this abuse. It is widely known that repeated use of certain drugs leads to habituation and with some drugs to addiction. In some cases the social and related effects of this addiction may be sufficient to indirectly lead to morbidity and death. In other cases actual pathological damage may result as is the case with **cocaine** which causes liver damage and may also destroy the nasal passages when inhaled. The toxic effects of **chronic alcohol abuse** on the liver and brain are widely known as are the many hazards of smoking **tobacco**. Both alcohol and tobacco are addictive drugs and cause far more widespread damage to public health than the more notorious hard drugs such as **heroin** and cocaine. Drug abuse also causes indirect effects on

human health, such as injury following driving under the influence of drugs, child abuse occurring as a result of drug use, and the AIDS virus spreading via intravenous drug users.

Summary and learning objectives

Drugs are biologically active molecules to which we are all exposed. They may cause toxicity after ***overdoses*** (e.g. paracetamol, aspirin) or after ***therapeutic doses*** (e.g. debrisoquine, hydralazine, halothane). Toxicity after overdoses is often but not always a ***predictable exaggerated pharmacological***, ***physiological*** or ***biochemical response***. Toxicity after therapeutic doses is often ***unpredictable***, maybe idiosyncratic and unrelated to the pharmacology.

Drug toxicity may be affected by genetic factors that alter disposition or susceptibility and environmental/lifestyle factors such as multidrug use or alcohol intake.

Drug toxicity also may be the result of interactions between two or more drugs or between a drug and another chemical.

Paracetamol causes *liver necrosis* after overdoses as a result of metabolic activation, depletion of glutathione and interaction of a reactive metabolite with cellular proteins. Toxicity may be increased by enzyme induction due to use/abuse of alcohol or barbiturates.

Aspirin toxicity is manifested as physiological and biochemical disturbances (metabolic acidosis, uncoupling of ATP production, rise in temperature, hypoglycaemia). This may follow accidental, suicidal or therapeutic overdosage, the latter resulting from saturation of elimination.

Hydralazine causes an *immunological toxicity* following long-term therapeutic usage particularly in susceptible individuals (female, slow acetylator phenotype, highest dose, HLA type DR4). This is manifested as a lupus erythematosus-like syndrome with joint pain, skin rashes and antinuclear antibodies.

Halothane also causes an *immunological toxicity* but one that is much more severe than hydralazine. The effect of this autoimmune type of toxic response is destruction of the liver which has a high fatality rate. As with hydralazine there are predisposing factors (female gender, multiple exposures, obesity, history of allergy). The toxicity involves metabolic activation of the halothane, subsequent interaction of the metabolite with liver cell proteins and a combination of antibodies and lymphocytes targeting and destroying liver cells.

The toxicity of **debrisoquine** involves effective overdose as a result of *genetic deficiency* in metabolism. The pharmacologically active parent drug is not metabolized in some individuals (approximately 6–8 per cent of Caucasians) leading to a predictable, exaggerated loss of blood pressure.

Thalidomide caused birth defects (phocomelia) when given to pregnant women for the treatment of morning sickness. It was relatively non-toxic to the women but a potent teratogen when taking during the critical days 24–29 of pregnancy.

Combinations of drugs may lead to unexpected toxic effects as a result of **drug interactions**. These may be due to interference with the metabolism of one drug by another (induction or inhibition), displacement from plasma protein binding sites, or alteration of the pharmacological response.

Drug toxicity may sometimes be due to **altered responsiveness** as is the case with **glucose-6-phosphate dehydrogenase deficient** individuals who suffer haemolytic anaemia as a result of exposure to drugs such as primaquine and some sulphonamides. These susceptible individuals lack the protective

glutathione in their red cells, making them prone to damage.

Questions

Q1. Select A if 1, 2 and 3 are correct
Select B if 1 and 3 are correct
Select C if 2 and 4 are correct
Select D if only 4 is correct
Select E if all four are correct

Adverse effects of drugs in humans may be caused by:

1 exaggerated pharmacological effects after overdoses
2 idiosyncratic effects after normal doses
3 toxicity unconnected to the pharmacological effect after inappropriate doses
4 interactions with dietary constituents.

Q2. Choose one answer which you think is the most appropriate.
Paracetamol is an analgesic drug that may cause liver damage after overdoses. This is the result of:

a depletion of body stores of sulphate
b inhibition of cytochrome P450
c production of a glutathione conjugate
d metabolic activation by the microsomal enzymes
e biliary excretion and metabolism by the gut bacteria.

Q3. Choose one answer which you think is the most appropriate.
Which of the following have been shown to be predisposing factors in the toxicity of hydralazine:

a genetic polymorphism of metabolism
b gender
c dose
d alcohol intake
e glucose-6-phosphate dehydrogenase.

Q4. Indicate which are true and which false.
Thalidomide is a drug which:

a only causes malformations in rats
b causes morning sickness in women
c causes phocomelia in babies when taken by pregnant women
d is only toxic if the R isomer is taken.

Q5. Indicate which are true and which false.
Halothane is a drug which:

a induces cytochrome P450
b destroys lymphocytes
c causes liver damage more commonly in female patients
d causes allergic reactions.

SHORT ANSWER QUESTION

Q6. Why are the plasma and urinary pH crucial in aspirin poisoning?

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