11

Developmental Pharmacology and Age-related Phenomena

11.1 Introduction

There is a saying: 'Children are not just small adults.' However, and paradoxically, this statement is often followed by a discussion of dosing based on weight, such as in mg kg^{-1} terms, as in classical pharmacology.

Interest in both the young and the old as special populations is now well established, especially in phenomena related to pharmacokinetics. Development of hepatic function and renal processes has received intensive study. Studies of drug responses, and of drug concentrations in body fluids, at different ages are commonplace. This reflects a dramatic change since the early days of clinical pharmacology. However, the study of extreme age groups remains hampered by severe limitations. For example, analytical methods suitable for the small blood samples obtainable from children have required specific development, and ethical problems persist for studies in both the very young and very old age groups.

A major problem has been dissociating effects of age itself from effects of age-related practices and phenomena, such as smoking, caffeine, alcohol and other drug consumption, and dietary and exercise habits. Also, age-related disease is an inevitable complication. There remains a great need for longitudinal studies in particular individuals, but the time required for such work is an obvious limitation. Any claim for an age-related observation must be interpreted in this light.

11.2 Scientific and regulatory environment in regard to younger and older patients

Awareness that there was a growing need to ensure that drug therapies for the paediatric population were studied with the same level of scientific and clinical rigour as adult therapeutic agents developed slowly between 1968 and 1998. In 1968, children were described by Shirkey as 'therapeutic orphans', but it was not until 1998 that the Food and Drug Administration (FDA) issued its 'Final Rule' on requirements for assessing safety and effectiveness in paediatric patients. Companies had been reluctant to study drugs in children because of the complexity, difficulty and expense of clinical trials in children, preferring to leave dosing recommendations to prescribers, who tended to assume that children merely required relatively low doses in order to respond similarly in the way that adults do. The result was empirical use of medicines without prior evidence-based efficacy and safety studies, with a high incidence of off-label or off-licence use of drugs (i.e. use in ways not approved by the relevant authorities). While often satisfactory for drugs for which there was a long history of experience, the outcome with newer drugs could be beneficial or harmful.

Legislative initiatives have catalysed a vast improvement in this situation, such that by 2009, the approved prescribing information on over 100 drugs had been brought up-to-date in regard to paediatric populations as

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the result of specific clinical studies designed to make this possible. The scientific hurdles that first had to be overcome included:

- Parent, and ethics committee/institutional review board (IRB) attitudes had to be changed from a basically negative stance to realization that studies in children were needed for the benefit of children.
- Experimental techniques in regard to frequency of sampling and volume of blood removed in pharmacokinetic studies required refinement.
- Specialized research units in tune with paediatric issues, both physical and psychological, needed to be established.
- Population pharmacokinetic protocols had to be developed. In these, relatively small numbers of samples from each individual, such as those collected at clinic visits, but from relatively large populations of children, permitted the use of scatter-plot graphs for identification of pharmacokinetic profiles.
- Ethical approaches to the protection of children with regard to vulnerability to coercion, as well as use of placebo controls, had to be established.

Similar considerations have driven growing interest in the geriatric population, although legislative influence has not been as strong. Older patients tend to have multiple diseases, including those affecting the organs involved in drug disposition and fate, experience a disproportionate incidence of drug interactions, have poor compliance, are vulnerable to coercion when they are involved and have traditionally been excluded from research protocols, or have not had available to them appropriately equipped research units where high quality protocols are adopted. The epidemiological approach to collection of research data has again been very valuable, especially with such initiatives as the Framingham study (Levy and Brink, 2005) and, as with children, population pharmacokinetics has assisted in scientific rigour.

11.3 Terminology

One difficulty in age-related studies has been in defining when a neonate becomes a child, when a child becomes an adult, and when an adult becomes elderly. This terminology has evolved to agreement on the following basic divisions of the segments of life for most purposes:

- Premature — born before anticipated date of full-term development
- Neonate — birth – 1 month
- Infant — 1 month – 2 years
- Child — 2–12 years
- Adolescent — 12–16 years
- Older adult — 65 and over.

11.4 Physiological and pharmacokinetic processes

11.4.1 Absorption

The pH of the stomach varies from 6 to 8 at birth, dropping to pH 1 to 3 within a few hours. This is followed by 8 to 10 days of virtual achlorhydria. Gastric acid secretion is lower in premature newborns. Gastric pH is again lower by day 30. Adult values of gastric pH are reached after approximately 3–5 years, but some literature suggests that it can take as long as 12 years for the complete adult pattern to emerge. In adulthood, the pH increases with age so that approximately 35% of persons over 60 have achlorhydria. Gastric emptying is prolonged in neonates, reaching adult levels at 6–8 months. Growth of intestinal flora progresses with

development. Biliary excretion and the splanchnic circulation show postnatal development and there is low bile acid secretion in newborns with implications for enterohepatic circulation involving conjugation and hydrolysis. In the elderly, there is a general delay in absorption of nutritional substances with age.

Intramuscular injections are subject to the changes in muscle blood flow, such as those which occur in the first days of life, and to temperature-dependent phenomena such as vasoconstriction. The high water content of the skeletal muscle mass may also be a factor.

The skin is more permeable to drugs in the newborn and the young, because of the thinner stratum corneum and greater hydration. This was shown to be very important when hexachlorophene was used when bathing babies, and remains an important reason for not using topical salicylic acid preparations, in particular in young children.

11.4.2 Binding and tissue distribution

Tissue distribution relates to body weight, and is obviously related to age as adults are larger than children. However, it is probably the proportion of particular constituents which is most important. The proportion of water in premature babies is as much as 85% of body weight. This drops to 55–75% in full-term babies, and 50–70% in adults. The extracellular fluid is 40% of body weight in neonates compared to 20% in adults. Adult values are reached at 10–15 years of age. The proportion of intracellular fluid (evident by calculation of differences) is relatively low at birth , but quickly reaches adult values which remain unchanged throughout the remainder of life – these differences are of no significance in dosing. The fat proportion increases with age and shows wide fluctuation at various stages in life. All of this will affect tissue-to-plasma concentrations ratios, for both lipophilic and hydrophilic drugs. Additionally, the relative acidosis of the newborn will affect the tissue distribution of weak electrolytes.

Protein binding can vary with age, although albumin concentrations are normal, total protein concentrations are lower in newborns. This implies that there are lower concentrations of proteins other than albumin in newborns. Adult values are reached at 10–12 months. This difference in binding, combined with a risk of high blood bilirubin concentrations consequent on immaturity of the conjugating systems, compounded by an immature blood-brain barrier, leads to the risk of kernicterus in the newborn being aggravated by drugs such as sulfonamides, which displace bilirubin from those binding sites that are available. Also in regard to binding, plasma free fatty acid concentrations, and also cholesterol, vary over a wide range and show age-related trends. These measurements are variously affected by diet, activity, obesity, caffeine and ethanol amongst other things. In fact, although some links between these measures and binding of drugs to albumin have been noted, no relation between, in particular, plasma free fatty acids and drug response connected with this appear to have been shown.

11.4.3 The blood–brain barrier

Whilst most of the basic structure of the human brain is formed before birth, neuron proliferation and migration continue into the postnatal period. The blood–brain barrier is immature at birth, reaching full development by about 6 months. Synaptic connections between neurons continue to develop in later years. At the other extreme of life, ageing of the microcirculation can result in significant alteration in the blood–brain barrier with function remaining intact, but with the susceptibility to disruption by external factors, such as hypertension and drugs, increasing. There is little evidence that overall transport functions change with age, but changes in select carrier-mediated transport systems in the blood–brain barrier definitely occur, such as with choline, glucose, butyrate and triiodothyronine. These age-related changes are the result of either alteration in the carrier molecules or the physicochemical properties of the cerebral microvessels. In regard to drugs, the specialized ‘tight-junctions’ and specific efflux mechanisms of the blood–brain barrier exclude most xenobiotics. In a small number of cases, drugs penetrate the brain via active transport. However, most

useful centrally acting drugs diffuse into and out of the brain, and this diffusion is unlikely to be much affected by age. The exact sum of these influences on any particular drug example may be complex, but the overwhelming evidence that both newborns and elderly people are especially sensitive to centrally acting drugs suggests that, on balance, the two extremes of age result in the reduced ability of the brain to exclude xenobiotics, as well as, perhaps, relatively high pharmacological sensitivity.

11.4.4 Liver function

The ratio of weight of liver to total body weight in children is 30–35% of that in adults, but then the liver becomes relatively smaller as people grow older. The important drug metabolic reactions that occur in adults are to be found at the extremes of age. However, there are some important differences. *N*-Methylation, the reverse of *N*-desmethylation occurs in children, but is virtually absent later in life. This results in the conversion of theophylline, once a popular treatment for childhood asthma, into caffeine, which is basically undesirable in children. Also, sulfation is especially well developed in children, resulting in relatively rapid metabolism of paracetamol (acetaminophen). Acetylation is slow in children.

The rat liver shows postnatal development reaching the adult substructure at 5–7 days. In contrast, the human foetal liver shows complete differentiation at the third month of gestation. The blood supply changes at birth. Concentrations of factors such as NADP, and other essential constituents of the P-450 system show complicated changes in early life. In one study, undifferentiated total P-450 concentrations were as high in human foetal liver as in adults. A major complication is the degree of enzyme induction that affects particular samples, depending on exposure of mother, foetus and baby to environmental chemicals, and to drugs. This is difficult to measure. Both pre- and postnatal enzyme induction occurs, and this has led to the use of phenobarbital as a treatment for problems caused by low levels of bilirubin elimination, which lead to neonatal jaundice resulting from low hepatic ability to form glucuronides, mentioned earlier, at birth. In contrast, the activity of β-glucuronidase may be sevenfold the adult level in neonates, with implications for enterohepatic circulation (Section 3.3.8.1).

In one study attempting to characterize this, the newborn of mothers treated with phenytoin showed an ability to metabolize the drug comparable with that of the mothers, and carbamazepine metabolism was faster than that in the mothers. In this regard, the need to compare neonatal metabolism with that of the mother, preferably by the use of cord blood, has been stressed. This is infinitely preferable to comparison of neonates with unrelated adults.

In humans, alcohol dehydrogenase is detectable at 2 months of gestation and reaches adult values at 5 years of age. In contrast, foetal liver has high steroid hydroxylating ability. Experimental animals vary in their patterns. For example, rats show high *N*-hydroxylating activity at 2–3 days and 27 days, but lower activity in between. Rabbits show increasing activity from birth onwards. In humans, hydrolytic activity (e.g. plasma esterases) and acetylation develop postnatally taking a few weeks to reach adult values. Reduction shows immaturity at birth, as does conjugation (glucuronidation, mentioned earlier, plus, paracetamol apart, sulfate and glutathione conjugation).

Elderly people show reduced liver activity as evidenced by lower clearance and longer half-life values for various drugs. It is presumed that reduction in protein synthesis as well as other factors, as discussed below, plays a part in this.

11.4.5 Changes in CYP-450 isoforms during the life cycle

While there is an abundance of information on drug clearance and half-life as a function of age, there is relatively little on the specific isoforms of the P-450 system in this context. The experimental approach to this topic includes *in vitro* work with liver samples from aborted foetuses, and/or postmortem dissections,

biopsies from adult donors undergoing abdominal surgery for unrelated reasons, and work-up of microsomes and RNA for measurement of activity and the study of mechanisms, plus *in vivo* work with specific probe substrates including 'cocktails' (Section 10.2.2.).

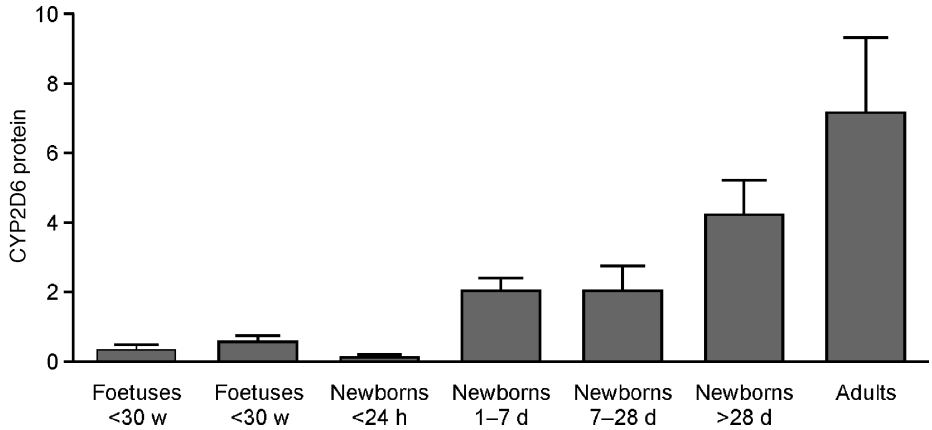

Figure 11.1 Age-related variation of CYP2D6 protein in human liver. Results are the mean ± s.e. mean of individual values. (After Treluyer *et al.*, 1991.)

One of the earliest studies relevant to this question was performed by Treluyer *et al*. (1991). Studying CYP2D6 and using dextromethorphan as a substrate, it was shown that activity rises in the first few weeks of life, regardless of gestational age. Figures 11.1 and 11.2 show the age-related variations in CYP2D6 protein in human liver in seven age groups, and also the age-related variations in CYP2D6 RNA in the same samples. Dextromethorphan metabolism correlated well with the data. It is striking that the protein concentrations increased across the life-span, but the RNA levels fell in the adult. This can be taken as indicating that regulation varies with age at the transcriptional level. Complementing this work, Agundez *et al*. (1997) studied DNA from blood cells, using standard PCR techniques and restriction fragment polymorphism methods. Their work particularly focussed on nonagenarians, and on three enzymatic polymorphisms that affect *CYP2D6*, *NAT2* and *CYP2E1* genes and the activity of their enzymatic gene products. The three

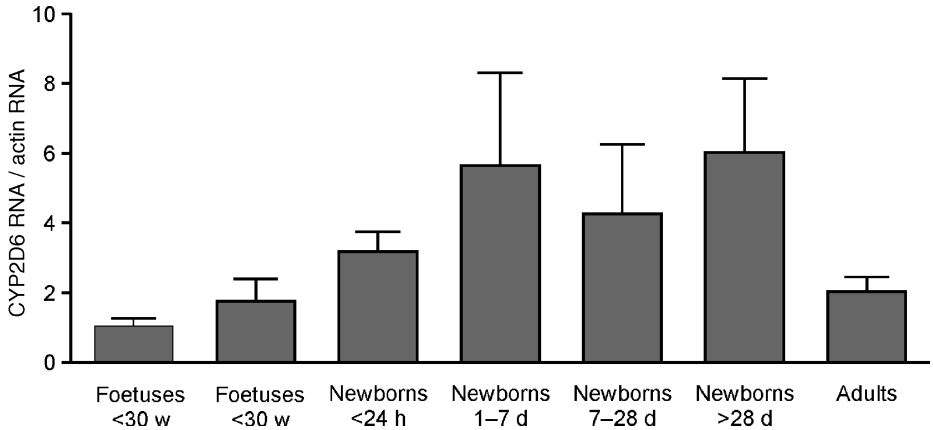

Figure 11.2 Age-related variation of CYP2D6 RNA in human liver (see Figure 11.1 for analogous information). (After Treluyer *et al.*, 1991.)

genotypes were compared in 41 nonagenarians and over 100 younger volunteers (mean age in their 30s). No qualitative or quantitative differences were found in the mutations underlying the three polymorphisms studied, nor in the expected enzymatic phenotypes. Thus longevity did not seem to be related to any special configuration of the traits studied.

Tanaka (1998a, b) reviewed the literature on changes in probe-drug metabolism by various isoforms of the cytochrome P-450 system at five stages in life: neonates (<4 weeks), infants (<12 months), children (<19 years), young/mature adults (20–64 years), and elderly adults (>65 years). The probe drugs included caffeine (CYP1A2), phenytoin (CYP2C9), amitriptyline (CYP2C19), paracetamol (CYP2E1) and midazolam (CYP3A4). Two marginally different patterns were identified: (i) activity low immediately after birth, then increasing to a peak in the young/mature adult, and then decreasing in old age (CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4); and (ii) activity increasing rapidly after birth to reach a level equivalent to that of the young/mature adult, then gradually decreasing, but decreasing more rapidly in the elderly (CYP2E1). These two patterns are not as dissimilar as they appear to be at first sight, and conform to existing ideas about the influence of age on drug metabolism.

Bjorkman (2005) constructed a physiologically based pharmacokinetic model, using theophylline and midazolam as examples, to cover the age range from birth to adulthood. Physiological data on such parameters as body weight and surface area, blood flow, and fluid spaces were used to calculate tissue : plasma partition coefficients using rat data. These data were compared with unbound fractions of the drugs in human plasma, and unbound intrinsic clearance was estimated for various age groups for CYP1A2, CYP2E1 and CYP3A4. Volume of distribution, renal clearance and elimination half-life data were estimated and compared with literature data. Predictions were generally good and the relationships between pharmacokinetic parameters and age reported in other literature were supported. Other more recent studies generally support the conclusions reached by Treluyer, Agundez, Tanaka and Bjorkman, including the existence of examples, such as metoprolol (Goryachkina *et al*., 2008) where there are apparently virtually no age-related changes. Thus observations of *in vivo* patterns of age-related pharmacokinetic parameters, protein concentrations and transcription factors, and physiological factors, such as hepatic blood flow, should permit rational future consideration of any particular age-related phenomenon in this context.

11.4.6 Renal function

A relatively small proportion of cardiac output reaches the kidneys in the very young. Also, there is relatively slow glomerular and tubular development, and the loop of Henle is incomplete. Glomerular filtration in human beings is immature at birth, but postnatal development is rapid, shown by inulin clearance usually reaching adult values at 2–3 days, although occasionally needing 15–20 days to reach maturity. Between one month and 20 years of age, glomerular function remains stable. For the age group 20–90 years, inulin clearance follows the formula:

$$CL_{\text{inulin}} = 153.2 - (0.96 \times age) \tag{11.1}$$

indicating a slow decline. However, it is more usual to assess kidney function using creatinine clearance (see Section 6.3.1.1). Creatinine distributes throughout total body water, shows little binding or tissue localization, and is eliminated almost entirely by renal excretion. However, it exhibits renal tubular movement equally in both directions, so while its clearance calculates glomerular filtration, it can be subject to changes in tubular activity, if for instance, the balance of movement in the two directions were to become disturbed.

Active tubular reabsorption and tubular secretion develop postnatally; in general transport maximum values are reduced in neonates. *p*-Aminohippurate (PAH) clearance reaches adult values at 25–30 days, but the range is 3–35 days. The mass of functioning tubular cells is reduced at birth, as are tubule length, blood flow to the peritubular area, and energy supply processes. In contrast, no age-dependent

differences in non-ionic diffusion have been noted, although the pH of the urine is somewhat reduced in neonates.

Creatinine clearance, normalized for body weight, is highly depressed in premature newborns, and is depressed in the neonate. However, it develops rapidly, reaching a maximum at 6 months, when it is twice the adult rate. Thereafter it diminishes at approximately 1% a year. From age 20 onwards creatinine clearance ($mL\,min^{-1}$) is given by the following formulae:

Males:

$$CL_{\text{creatinine}} = \frac{(140 - age) \times W}{70} \tag{11.2}$$

Females:

$$CL_{\text{creatinine}} = \frac{(140 - age) \times W}{85} \tag{11.3}$$

where *age* is in years and *W* in kg.

In the practice of medicine it is not uncommon to use serum creatinine measurements to estimate creatinine clearance, avoiding the need for urine collection. These estimates are prone to error, actually leading to underestimates of renal clearance, as serum creatinine reflects both production and elimination of creatinine, but they serve many diagnostic needs. Clearly, in the relatively simple case of a drug, such as gabapentin, that is excreted unchanged, it is thus possible to calculate an appropriate dose that allows for the decline in renal function with age using serum creatinine as a guide. This appears to be rarely done in such a systematic way, although empirically, these scientific facts affect the thinking behind prescribing practices. There are other physiological functions that decline with age at about the same rate as renal function, affecting measurements of cardiac and respiratory function in particular. Clearly, these are functions that can affect drug disposition.

The development of the renal elimination processes is presumed to underlie the changes in the half-life of ampicillin in neonates and infants shown in Table 11.1, which would dictate the use of relatively small doses of ampicillin in neonates, and the relatively high doses of tobramycin sometimes proposed for use in older children (see Section 11.5).

Table 11.1 Half-life of ampicillin in four groups of neonates and infants aged between 2 and 68 days following intramuscular doses of $10\,mg\,kg^{-1}$ (Axline *et al.*, 1967)

Age range (d)	Mean half-life in serum (h)
2–7	4.0
8–14	2.8
15–30	1.7
31–68	1.6

NB Ampicillin is excreted unmetabolized.

11.4.7 Metabolic and pharmacodynamic phenomena

It is to be expected that drug responses might vary with age as the result of pharmacodynamic sensitivity or metabolic differences. However, compared with the abundance of pharmacokinetic data, examples are few. Among those available, salicylates cause metabolic disturbances in all age-groups, but the disturbance can be especially great in children under one year of age. Disturbances in acid-base balances

are easily provoked in young children, and this has implications for the use of electrolytes in pharmacological procedures. Many diuretics act selectively by reaching concentrations in the kidney higher than those elsewhere, and because filtration and tubular phenomena are not fully developed in neonates, this selective action can be less easily obtained for both pharmacokinetic reasons (see earlier) and also because the maximum effect obtainable on Na^+ transport, which is the basis for action of many diuretics, is less in the neonate. This can, in turn, lead to the need for higher diuretic doses for a standard effect in young patients.

11.5 Body surface area versus weight

Small objects have greater surface area in relation to volume than do large objects. This includes small people. The use of body surface area for normalizing doses across the life span is frequently mentioned. However, it is used relatively rarely. The concept can actually be traced back for over 150 years. The relationship between surface area, weight and height is given by the equation (amongst others):

$$S = W^{0.425} \times H^{0.725} \times 71.84 \tag{11.4}$$

where S is body surface area in square metres, W is body weight in kilograms, and H is height in centimetres. This can be logarithmically transformed to:

$$\log S = 0.425 \log W \times 0.725 H \times 1.8564 \tag{11.5}$$

to permit straight line plotting. This relationship was determined by Dubois and Dubois in 1916.

Nomograms exist permitting this information to be used to calculate surface area from height and weight for any individual. These nomograms have been reprinted in multiple publications, such as textbooks of paediatric clinical pharmacology, and the Documenta Geigy Scientific Tables. Clearly, surface area increases with increases in weight and height. In fact, the increase in surface area with age is linear, and there are good correlations between surface area and cardiac output, renal blood flow, and glomerular filtration rate. These correlations are better than those with body weight. The ratio of surface area to weight decreases with height and weight, and the ratio of surface area to height increases with height and weight. The concept is that therapeutic precision would improve if doses were related to surface area rather than weight.

As a practical example, while ciclosporin is usually dosed on the basis of weight in adults, starting with an i.v. dose of approximately $3\,mg\,kg^{-1}$, dosing in children starts with either $2\,mg\,kg^{-1}$ or $60\,mg\,m^{-2}$ i.v. In a 27.2 kg (60 lb) child, $2\,mg\,kg^{-1}$ is 54.4 mg, and Figure 11.3 compares this with doses calculated on the basis of $60\,mg\,m^{-2}$ in five theoretical individuals weighing 27.2 kg (60 lb.), but with heights varied from 76 to 137 cm (30 to 54 inches). The highest of these doses is over 50% more than the lowest. The highest of these doses is over 50% more than the lowest. In practice, dosing on the basis of body surface area is limited almost entirely to the field of cancer chemotherapy, and then to children, where i.v. administration is widely used. A variation on this is incorporation of creatinine clearance into the calculations, to allow for the variations in renal function. Beyond this, perhaps with the possible exception of the prescribing of potentially toxic i.v. antibiotics, the use of body surface area in calculating doses appears to be positively discouraged by authorities such as the American Academy of Pediatrics, at least in part because it can lead to prescribing of drugs in ways different from those approved by the FDA. There seem to have been few, if any, systematic studies of human pharmacokinetic parameters as a function of body surface area, because, by definition, the new drug discovery system seeks new chemical entities that show linearity with weight in their drug dispositional properties.

However, some nursing literature still recommends the use of weight for premature and full-term neonates, and surface area for children.

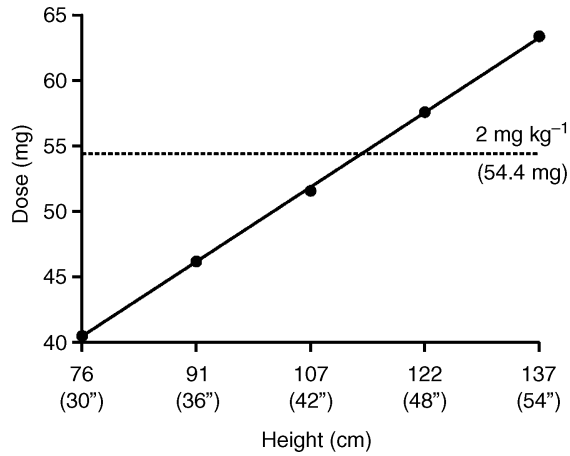

Figure 11.3 Ciclosporin dose (mg) calculated on the basis of surface area for five individuals weighing 27.2 kg (60 lb) and ranging in height from 76 cm (30 inches) to 137 cm (54 inches); the dashed line is the dose in mg that would have been given on the basis of weight alone (2 mg kg^{-1}).

Only for one of the drugs, sotalol, studied in the Paediatric Initiative (Section 11.2) was body surface area shown to be an important covariate. Smaller children (body surface area <0.33 m^2) showed a tendency for a larger change in the QT interval (QTc) and an increased frequency of prolongation of the QTc interval, as well as greater β-receptor blocking effects, so that it is considered that the best therapeutic approach with this drug is individualized dosing based on body surface area.

11.6 Age groups

11.6.1 Neonates and children

Summarizing from the foregoing, very young children show changes principally in metabolism, excretion and the blood–brain barrier, plus pharmacodynamic sensitivity. As an example, interesting data have been presented for ampicillin. Table 11.1 shows mean half-times in four groups of infants of various ages. The drug was excreted slowly by the youngest infants. As this drug is dependent for its removal from the body on excretion by the kidney, it is immediately obvious that this is an example of an immature kidney at birth. Both glomerular filtration and active tubular secretion are immature in the newborn and excretion of ampicillin is dependent on both of these processes. In addition to the data quoted in the table, two other observations are important. First, the half-lives for the drug in serum were studied in the same patients at different ages – that is serially. The serum half-lives always declined, reaching a steady value around 15 days, independent of the weight or gestational age of the infants. This suggested that the maturation is purely a postnatal phenomenon and is possibly a substrate-dependent enzyme induction phenomenon, of either an enzyme or of a tubular transport protein.

As discussed earlier, children, as opposed to newborn infants, have mature systems for handling drugs, but children are of course smaller than adults. Over the years a number of different systems have been devised for calculating the doses of drugs to be given to children. These doses are usually a fraction of the adult dose, dependent on the age and weight of the child, with the full adult dose being introduced at puberty.

11.6.2 Elderly

There is a general presumption that the aged are unusually sensitive to drugs, and that this may be caused by subclinical impairment of cardiac output and hepatic and/or renal function associated with old age. Certainly, clinical evidence seems to show that the elderly are especially sensitive to drugs, so that the idea of increased sensitivity is now unquestioned. The principal factors seem to be liver and kidney impairment, and also a pharmacodynamic contribution, such as increased central nervous system (CNS) sensitivity. The difficulty arises when there is no clinical evidence of impairment of elimination. Other factors such as loss of weight and changes in perfusion of tissues perhaps caused by atherosclerosis, as well as target organ sensitivity outside the context of CNS sensitivity probably play a part. Changes in neurotransmitter concentrations with ageing will lead to differences in drug response both centrally and peripherally. The drug examples below illustrate key points to consider in this population.

Warfarin has been vigorously investigated in relation to age. At the same plasma warfarin concentration there was a greater inhibition of vitamin K dependent clotting factors in elderly people, but this was accompanied in at least one study by no important differences in pharmacokinetics, even though there was reduced plasma albumin and reduced binding to plasma proteins. In an analogous study, the rat was used as an animal model to show that the major difference on ageing is sensitivity of the target organ (Shepherd *et al*., 1977).

Nitrazepam, although now virtually obsolete in modern therapeutics, was so fully investigated, that it remains of interest as a model compound, as it was at one time a compound of considerable concern in regard to its safety in elderly people. The aged experienced more unwanted CNS depression from this drug than did other people. In one particular well-controlled study the peak concentration was lower, the volume of distribution was higher, and the terminal-phase half-life was unexpectedly shorter in elderly people who had a wide variety of pathology including heart failure, leukaemia and diabetes. In contrast, in another study, no differences were seen between healthy young and old persons, and in yet other studies a prolonged half-life has been recorded in older people – this latter observation has become the most prevalent one. Protein binding and clearance studies have shown equivocal results. There was a difference in response in both of the initial studies, indicating that: (a) that the elderly are more sensitive pharmacodynamically; and (b) pathology is more likely than age to be the reason for the pharmacokinetic changes (in general, the apparent volume of distribution increased, for reasons that are not entirely clear, leading to delayed elimination) (Greenblatt and Allen, 1978).

Lithium has been thoroughly investigated. There were significant correlations between daily lithium dose and age over a wide range, and also between measured lithium concentration and age, probably because of age-related reductions in renal clearance. However, the dose dropped by only 45% over a 60-year scale, and levels dropped by only 23%. On average, the 80-year-old required only two-thirds the dose required by a 20-year-old to obtain the same concentration. The correlation for this relationship was *statistically* significant, ($r = -0.2354$, $p < 0.05$; $n = 82$); however, as $r^2 = 0.055$, the effect of age accounts for only 5.5% of the variation in concentration. Thus, the clinical significance is slight (Hewick *et al*., 1977).

Phenytoin was similarly studied. In a carefully evaluated program, serum phenytoin was correlated positively with age according to the equation:

$$\begin{gathered}\log(\textit{serum concentration}) = 1.471 + 0.0046\,\textit{age} + \textit{residual error} \\ r = 0.31,\ t = 4.1,\ p<0.001\end{gathered} \tag{11.6}$$

The increase in concentration was a result of a reduction in V_{max} with age. The study which included measurement of weight, sex and height, as well as age, in epileptic patients, concluded that adjustment

of the dosage according solely to age of a patient would achieve only a marginal improvement in therapy. In any case, phenytoin serum concentrations are routinely monitored during therapy (Houghton *et al*., 1975).

11.7 Further examples

Data on variations in pharmacokinetics with age have now been collected on hundreds of drugs and published in thousands of papers. Data compilations such as those in *Goodman and Gilman's The Pharmacological Basis of Therapeutics* tend to present data on age effects on 50% of the drugs listed, with multiple observations on each drug (e.g. on bioavailability, clearance, volume of distribution, half-life, etc.). Often, where no effect of age is listed, it is because no studies have been conducted, not necessarily because there is no effect. Two observations stand out as illustrating trends:

- For both the young and the old, data are often equivocal, with both decreases and increases in pharmacokinetic parameters documented, along with greater variance than occurs in the reference adult population.
- The single most common observation in these various special populations is reduced clearance in both the young and the elderly, with consequent increases in half-life.

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12

Effects of Disease on Drug Disposition

12.1 Introduction

Drug responses are affected by disease states because of changes in both pharmacokinetics and pharmacodynamics. This is especially apparent with diseases that affect the processes of drug disposition and pharmacokinetics – absorption, protein binding, metabolism, and excretion. However, our ability to reach conclusions concerning general principles has historically been impaired by specific difficulties:

- Diseases rarely occur in isolation, and categorization of patients as being in one particular disease group is simplistic in approach. For example, liver disease can lead to compensation by renal activity, and vice versa, or both can be impaired in parallel. Experimental difficulties arise with studies of one excretory organ when another one is involved as a complicating factor but not studied.
- It may be difficult to analyse for single factors. Subdivision of liver disease is a case in point – in many of the early studies it was rare to find a study restricted to one of: (i) acute viral hepatitis; (ii) cirrhosis; (iii) drug induced hepatic disease; or (iv) other problems.
- Diseases commonly occur at particular stages in life and therefore it can be difficult to separate the effects of disease on pharmacokinetic properties of drugs from such factors as age.
- Patients in disease groups are commonly treated with drugs that affect each other, such as enzyme-inducing agents, as well as several drugs at any one time. For example, patients with liver disease are likely to have been treated with a large number of drugs including sedative drugs that complicate objective assessment of any central nervous system (CNS) impairment caused by the disease.
- Measurements can be more difficult to make in patients compared with healthy controls because of the complexity of the scientific problem involved and the extent to which intervention in the life of a patient is possible.
- Longitudinal studies are needed, using the pre-disease subject as his or her own control. Also, studies are often at different stages of what is sometimes referred to as 'decompensation' and this has not, in the past, been adequately recorded in the literature.
- Studies with diseased patients can raise ethical questions that do not apply to control subjects.
- Some drugs are designed to utilize healthy organs to relieve influences on diseased organs, for example the use of diuretics to reduce the fluid load on the heart, while others are designed to reverse pathology at its site, for example the use of oral hypoglycaemic drugs to modify insulin utilization.

Effects of disease should be assessed in terms of the mechanisms of drug disposition and assessments of changes in drug plasma concentrations, as outlined in other chapters concerned with special populations and situations, such as age (Chapter 11), and drug interactions (Chapter 17).

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12.2 Gastrointestinal disorders and drug absorption

12.2.1 General considerations

It is to be expected that gastrointestinal pathology will affect drug response by changing drug absorption. However, the pattern for any condition is complex. For example, changes in pH do not necessarily affect absorption because of the relation between pH, site of absorption, gastric emptying, and such. Similarly, in coeliac disease multiple changes occur, including increased rate of gastric emptying, increased gastric acid secretion and prolonged reduction in pH after eating, reduced surface area for absorption, increased permeability of the gut wall, and deceased local enzyme concentrations. These factors interact to accelerate or decelerate absorption, and it is not surprising that a mixed pattern of changes has been reported.

12.2.2 Inflammatory conditions of the intestines and coeliac disease

Inflammatory bowel conditions include Crohn's disease and ulcerative colitis. Their cause is basically unknown. They are characterized by abdominal cramps and diarrhoea. Crohn's disease affects the full thickness of the intestinal wall, most commonly occurring in the lower part of the small intestine, and in the large intestine. In contrast, ulcerative colitis affects only the large intestine, and does not affect the full thickness of the bowel wall. Crohn's disease is especially common in young people, and is associated with inflammatory conditions of organs other than the gastrointestinal tract, such as the eyes and joints. Inflammatory diseases have the potential to change the surface area available for absorption, the thickness of the intestinal wall and therefore the distance over which diffusion takes place, intestinal pH, mucosal enzymes that metabolize drugs, intestinal microflora, gastric emptying and peristalsis, and transporters that control inward and outward movement of nutrients and drugs. It is not surprising therefore that a variety of different observations has been made with various drugs in these conditions. For example, in Crohn's disease, the absorption of clindamycin and propranolol has been shown to be increased in extent, while that of many other drugs is decreased. The production of α_1-acid glycoprotein (AAG) is increased. The expression of CYP3A4 and P-glycoprotein (P-gp) levels were significantly higher in biopsy samples from a group of children with Crohn's disease compared with controls. These differences could account for decreased bioavailabilities. An *in vivo* study with radiolabelled prednisolone in adults showed reduced bioavailability in Crohn's patients (on the basis of urinary excretion and *AUC* measurements). Faecal excretion was greater in Crohn's patients. In the case of paracetamol (acetaminophen), the mean rate constant of absorption was not reduced in Crohn's disease, the conclusion being that any pharmacokinetic differences that occurred were related to slower gastric emptying. Similarly, absorption of trimethoprim, methyldopa, and lincomycin has been shown to be reduced while that of sulfamethoxazole was increased. Enhanced absorption of macromolecules has been observed in Crohn's disease (e.g. horseradish peroxidase) using biopsy samples and *in vitro* methods of study.

Thus it can be anticipated that a drug dependent on passive diffusion is likely to be relatively slowly absorbed in these patients, while a drug heavily affected by mucosal CYP3A4 or P-gp might show highly variable absorption. A drug affected by gastric emptying might be expected to show delayed absorption, for example methyldopa, which showed reduced plasma levels of both the parent drug and one of its metabolites in Crohn's patients, which was attributed to slower gastric emptying (Figure 12.1). In contrast, in coeliac disease, the parent drug concentrations were also reduced, but metabolite concentrations were increased, suggesting stimulation of intestinal mucosal drug metabolizing enzymes. Also, as mentioned earlier, in coeliac disease there is an increase in the rate of gastric emptying. Table 12.1 summarizes a number of observations regarding gastrointestinal pathology and drug absorption.

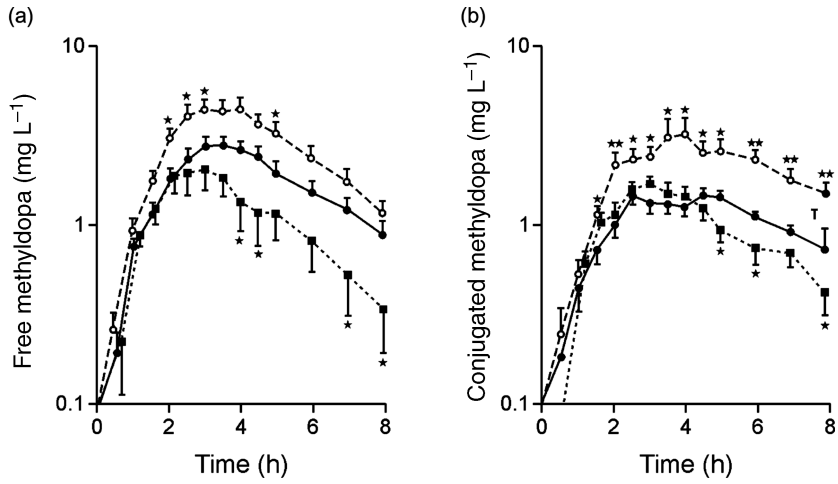

Figure 12.1 (a) Plasma concentration of methyldopa and (b) conjugated methyldopa after a single oral dose in normal subjects (•), patients with coeliac (○) and Crohn's disease (▪). Values are mean ± SEM, $^{*}p < 0.05$, $^{**}p < 0.001$. (Redrawn from Renwick *et al.*, 1983.)

Table 12.1 Some examples of influences of gastrointestinal pathology on drug absorption

Condition	Drug(s) affected	Nature of effect
Prolongation of gastric emptying	L-dopa	More than usual destruction by gastric acid
Achlorhydria	Aspirin and cefalexin	Impaired absorption because of pH effects
Gastric stasis/pyloric stenosis	Paracetamol	Impaired absorption
Shigella gastroenteritis/fever	Ampicillin and iron	Impaired/reduced absorption
Malabsorption syndromes	Tetracycline and digoxin	Absorption reduced
Biliary tract disease	Cefalexin	Reduced bile secretion affects solubilization prior to absorption
Coeliac disease	Many drugs	Examples exist of both decreased and increased absorption (see text)
Mucoviscidosis	Cefalexin	Decreased absorption
Crohn's disease	Many drugs	Examples exist of both decrease and increased absorption (see text)
Diarrhoea in children	Ampicillin/co-trimoxazole	Impaired absorption/no change
Gastroenteritis in children	Sulfonamides	Decreased renal clearance resulting from relative acidosis

12.3 Congestive heart failure

In congestive heart failure (CHF) the cardiac output (the volume of blood pumped per minute) is reduced so that insufficient quantities of oxygen and nutrients are delivered to the tissues for their normal functioning. Associated with CHF are atrial fibrillation and flutter, which are disorders of the electrical discharge patterns of the heart, causing relatively fast atrial contraction, and also causing the ventricles to contract more rapidly and less efficiently than normal. There are obviously many other disorders of the heart that affect patient health – for pharmacokinetic purposes the primary need is to focus on reduced perfusion of the organs that are

involved in the pharmacokinetic processes of absorption, tissue distribution, metabolism, and excretion, caused by reduced cardiac output.

12.3.1 Altered intestinal function

Chronic heart failure patients showed increased bowel wall thickness in the terminal ileum, the ascending colon, the descending colon, the transverse colon, and sigmoid (pelvic) colon. Increases in intestinal permeability to carbohydrates have been observed on the basis of observations of the lactulose/mannitol ratio and sucralose excretion. A relatively low level of D-xylose absorption has been taken to indicate occurrence of bowel ischaemia in CHF patients There are higher concentrations of adherent bacteria in the bowel mucous of CHF patients. CHF can cause inflammation in the gut. There are obvious implications for these changes on drug absorption, but they appear not to have been tested. Methods available for this are transcutaneous sonography, chemical assays, and biopsy samples.

12.3.2 Altered liver blood flow

There is a general supposition that CHF must reduce the rate and possibly the extent of tissue penetration by drugs. This has been investigated, for example, with lidocaine. The apparent volume of distribution of the drug was reduced, but no changes in the terminal-phase half-life were seen. Relatively high plasma levels were therefore recorded. A similar drop in the volume of distribution of procainamide has been noted. Another interesting observation with lidocaine was that the active metabolite, desmonomethyl lidocaine accumulates in the plasma in CHF, leading to CNS toxicity. Because lidocaine metabolism is limited by hepatic blood flow, which is lowered in heart failure, the explanation for this has to lie in lessened metabolism. However, at first sight the accumulation of the metabolite as a consequence of this is difficult to understand, but it may be that the pathological effect also leads to reduced further metabolism, and indeed, reduced renal excretion, of the metabolite.

12.3.3 Altered rate of metabolism – aminopyrine

In one of the earliest studies of CHF and pharmacokinetics, aminopyrine (amidopyrine) was used as a test substance with its metabolically-labile methyl group labelled with ^{14}C. (Hepner *et al*., 1978). Desmethylation leads to the radioactivity appearing in exhaled air, as ^{14}C-carbon dioxide and/or ^{14}C-formaldehyde. In the patients, 2.6% of the dose was recovered in this way, compared with 5.6% in healthy volunteers. Also, the total body clearance of the aminopyrine was 29.7 mL min^{-1} in CHF compared with 125.1 mL min^{-1} in the controls. The apparent volume of distribution was greater (63.6 L) in the patients compared with the controls (43.6 L). The breath test values also correlated with clinical improvement in response to treatment. This test, as a general method of investigation of drug metabolism, is further discussed in the liver disorders (Section 12.4).

12.3.4 Altered route of metabolism – glyceryl trinitrate

CHF patients often require higher doses of glyceryl trinitrate (GTN, nitroglyerin) for a useful effect. This drug has two pathways of metabolism, a high-affinity pathway operating in the nanomolar concentration range, in which 1,2-glyceryl dinitrate (1,2-GDN) is formed, and a low-affinity pathway operating in the micromolar range, in which 1,3-glyceryl dinitrate (1,3-GDN) is formed. The hypothesis that at a given GTN-induced blood pressure reduction, the CHF group would present with higher GTN concentrations, and

decreased 1,2-GDN/GTN and 1,2-GDN/1,3-GDN ratios in comparison with healthy subjects, was validated. Patients with CHF have attenuated GTN responsiveness (i.e. they require more GTN for a given clinical effect) and decreased relative formation of 1,2-GDN compared with controls, showing altered biotransformation in CHF.

12.3.5 Altered clearance – mexilitine

The apparent oral clearance (*CL*/*F*) was calculated from serial serum mexilitine assays in a large number of patients, 210 with CHF and 374 non-CHF controls. The ratio was reduced in the CHF group ($0.264 \pm 0.093\ \mathrm{L\,h^{-1}\,kg^{-1}}$ compared with control values of $0.393 \pm 0.082\ \mathrm{L\,h^{-1}\,kg^{-1}}$; data are mean $\pm$ SD, $p < 0.05$), indicating a difference in hepatic and/or renal activity towards the drug, resulting from blood flow and/or enzyme activity differences. There could also have been differences in bioavailability. The patients were sorted by New York Heart Association (NYHA) class into four groups. There was a relationship between the ratio and the NYHA class as an objective measure of severity of CHF, with CL_{Oral} being lower in patients in the class representing the higher level of CHF (Kobayashi *et al*., 2006).

12.3.6 Congestive heart failure plus renal problems – toborinone

The pharmacokinetics of toborinone were studied in patients with CHF and concomitant renal and/or hepatic disease. Glomerular filtration rate was measured using sodium iothalamate (amidotrizoate, diatrizoate) clearance and hepatic function was measured using a caffeine metabolism test. Indocyanine green clearance was also measured (Section 12.4.3). There were four test groups: CHF alone, CHF plus renal disease, CHF and hepatic disease, and controls. No significant differences were observed among the four groups in pharmacokinetic parameters. However, systemic clearance correlated with various measures of hepatic and renal impairment. For example, *CL* was reduced in parallel with reduced creatinine clearance, glomerular filtration rate, indocyanine green clearance, desmethylation activity, and liver blood flow.

12.3.7 Decompensated and treated CHF – torasemide

Members of a group of 12 CHF patients were given test doses of torasemide (torsemide) before and after haemodynamic parameters and clinical signs and symptoms of decompensated CHF were resolved. Plasma drug and urinary sodium concentrations were measured. Before resolution of the pathology, urinary sodium levels and urine output were relatively high. A significant increase in torasemide *AUC* occurred as the result of the treatment. However, there were no significant increases in the maximal excretion rate of the drug between the two test doses. Thus, CHF status had an impact on the pharmacokinetics of the drug, and on the relationship between plasma levels and effect, but did not affect the maximal excretion rate of the drug. It is of interest that there is an analogy in this with liver disease (Bleske *et al*., 1998).

12.3.8 Oedema

It is particularly difficult to determine whether any pharmacokinetic changes in oedema are caused by the underlying disease or by the oedema itself. For example, frusemide (furosemide) has been well studied in this context, as it is the drug of choice for rapid reversal of oedema in both CHF and renal failure. The rate of absorption of oral doses has been shown to be decreased in oedema of CHF although with no change in bioavailability – $C_{\max}$ values were generally decreased although paradoxically the time to achieve $C_{\max}$ was described as 'reduced or unchanged' (Vrhovac *et al*., 1995). Plasma protein binding of this drug is decreased

in CHF, decompensated liver disease, and nephrotic syndrome, probably because of hypoalbuminaemia. The elimination half-life can be unchanged, as in CHF and in cirrhosis, or prolonged, as in the oedema of chronic renal failure. Thus the pharmacokinetic changes are thought to relate to the diseases, rather than the oedema.

Digoxin is also of interest in relation to oedema, although, apart from expressions of much-needed caution in its dosing in oedematous patients, because of its narrow therapeutic window, no clear picture is available. However, it is reasonable to conclude that the large interindividual differences that occur in the pharmacokinetic properties of this drug in oedematous CHF patients relate in some way to variations in its volume of distribution, and to the reduction in oedema consequent on its use affecting this apparent volume of distribution. When evaluating digoxin kinetics it is important to assess whether the plasma concentrations could have been inflated by cross-reaction with digoxin-like immunoreactive substances, DLIS (Section 19.1.4).

Digoxin, and also frusemide, as treatments for oedema, provide opportunities for longitudinal studies with 'before and after' pharmacokinetic investigations. In contrast, this has not been the case with theophylline, which has shown a higher bioavailability accompanied by reduced clearance and a longer half-life in oedema associated with CHF, probably connected with liver blood flow changes. Study of this drug at the same time that an oedema-reducing drug was given would obviously be possible.

12.4 Liver disease

12.4.1 Pathophysiology

Cirrhosis is destruction of normal liver tissue leaving non-functioning scar tissue surrounding areas of functioning liver tissue. Many conditions can lead to cirrhosis, including alcoholic liver damage and chronic hepatitis. Basically, this is a progressing problem. *Hepatitis* is inflammation of the liver. It can be caused by viruses and/or chemicals, and can be acute or chronic. *Jaundice* causes a yellow discoloration of the skin and whites of the eyes, resulting from an increase in bilirubin in blood. One source of jaundice is *cholestasis*, or a reduction or stoppage of bile flow (obstructive jaundice). *Ascites* is fluid in the abdominal cavity, associated with liver disease, especially cirrhosis. There is also *liver encephalopathy*, or impairment of CNS function associated with liver disease, and, as a result of any kind of liver disease, there may be changes in liver blood flow as caused by '*shunts*' opening up to functionally replace blood vessels serving damaged liver tissue. The word 'decompensation' is used to indicate the gradual loss of liver function. There is an 'intact' liver theory, which states that chronic liver disease is associated with a reduced number of hepatocytes that function normally, and are normally perfused, as well as with the development of intrahepatic portosystemic shunting.

12.4.2 Liver blood flow, binding to plasma proteins, and intrinsic hepatic clearance

Liver disease can affect liver blood flow, creating the potential for effects on drugs with high extraction ratios such as propranolol and lidocaine, or hepatic intrinsic clearance, creating the potential for effects on drugs such as metoprolol, and (as the binding proteins are synthesized in the liver) on plasma protein binding, creating the potential for effects on warfarin and naproxen. Pharmacokinetic assessment should employ the equations presented in Chapter 7, with particular emphasis on the following two equations that apply to situations in which the percent protein bound is above or below 90%:

$$CL_{\mathrm{H}} = Q_{\mathrm{H}}E \tag{7.8}$$

$$CL_{\mathrm{H}} = Q_{\mathrm{H}}\left(\frac{f_{\mathrm{u}}CL'_{\mathrm{int}}}{Q_{\mathrm{H}} + f_{\mathrm{u}}CL'_{\mathrm{int}}}\right) \tag{7.17}$$

and the simplifications that can be made with this equation when the extraction ratio is below 0.3 or above 0.7 (Section 7.4.1).

Another equation can be useful in this context if it can be shown that all of an orally administered dose is absorbed into the intestinal epithelium cells and hence passes into the portal circulation:

$$CL_{\text{Oral}} = \frac{CL}{F} = \frac{D}{AUC} = f_{\text{u}} CL'_{\text{int}} \tag{12.1}$$

i.e. when $F = 1$, see Equation 7.18.

Verbeeck (2008) has emphasized the importance of *unbound clearance* for drugs with protein binding greater than 90%, and has also expressed the opinion that there is no great need for consideration of hepatic models of any complexity greater than that of the homogeneous single pool model in this context.

12.4.3 Methods of investigation

- The standard alanine transaminase and aspartate transaminase (ALT/AST) clinical laboratory tests are included in the standard chemical screen used by doctors to test the general health of a broad range of patients, even in routine physical examinations. They test liver function, and to a lesser extent heart, muscle and brain function, but no relationship with drug metabolism is apparent.
- The Child–Pugh score utilizes information on serum bilirubin and albumin, prothrombin time, encephalopathy, and ascites, each classified into three groups based on the levels of severity, to generate a score that assesses decompensation as it occurs over time while liver disease progresses. The score rises from ≤ 4 (effectively normal) to 10–15 (severe disease). It does not take into account any contribution from glomerular filtration. The clearances of several compounds have been correlated with Child–Pugh values. These include caffeine and erythromycin, but there is no obvious general pattern. There is another similar test (MELD) that takes serum creatinine into consideration, and is effective in predicting three-month mortality in patients awaiting liver transplants.
- Indocyanine green (ICG) is almost entirely eliminated through the bile. It has a relatively high extraction ratio (0.5–0.8) and its clearance changes with hepatic blood flow. It is given intravenously, and there is a correlation with severity of liver disease and also indicators of liver function such as bilirubin concentrations and prothrombin time. However, ICG clearance has not been shown to be superior to the Child–Pugh score.
- Galactose is also a convenient compound with a high extraction ratio. It has been known to show impaired clearance when given intravenously to liver patients and so to provide an indication of the severity of the disease. More recently, a single point method, based on the plasma concentration at the end of an infusion was shown to correlate with a wide variety of indicators of liver function, including AST and ALT, serum bilirubin, albumin, and prothrombin time. The galactose concentration was relatively high in patients with chronic hepatitis, cirrhosis, and hepatocellular carcinoma, compared with that in healthy volunteers. Several drug studies have shown a correlation between the galactose single-point (GSP) method of assessment and pharmacokinetic parameters, such as promazine clearance (Figure 12.2). The broader applicability of this method remains to be determined.
- Metabolic cocktails are used for assessing the various isoforms of CYP450 ('metabolic liver cell dysfunction tests'). At one time, antipyrine was widely used to non-specifically assess P-450 *in vivo*. Antipyrine is well absorbed, heavily dependent on microsomal metabolism for its clearance, has very low plasma protein binding, and has a volume of distribution equal to that of of body water. It has a low extraction ratio. Antipyrine has been superseded by the use of various more specific substrates for the various isoforms of P-450 (Table 10.2). The technique is applicable in liver disease as in age and other special population studies.
- Lorazepam is used in much the same way as the metabolic cocktail but as an assessment of glucuronide formation.

- Biopsy samples have been used in the study of glucuronyl transferase, sulfotransferase, acetyltransferase and glutathione transferase and correlations observed between conjugation of model substrates such as 2-naphthol, *p*-aminobenzoic acid, and benzo(a)pyrene-4,5-oxide, and severity of liver disease (Figure 12.3). There are obvious implications for drugs eliminated primarily by conjugation, and for metabolites of drugs that undergo phase I drug metabolic reactions.
- Ultrasound and electromagnetic methods for measuring liver blood flow also exist.

It should be obvious that there is no easy laboratory test that is sufficiently non-invasive and general in its application to fulfil the role that creatinine clearance fulfils in the case of renal disease (Section 12.5.2).

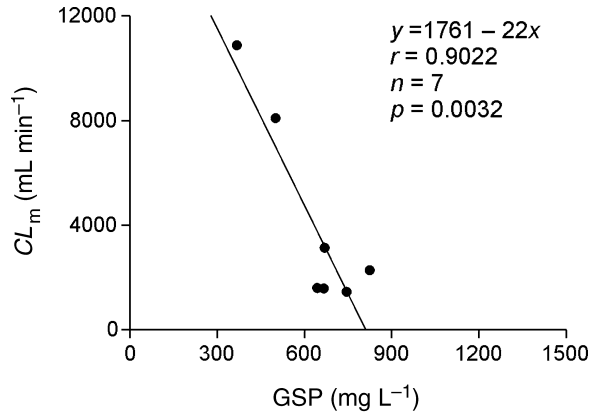

Figure 12.2 Correlation of unbound metabolic clearance of promazine with galactose single point determination (GSP).

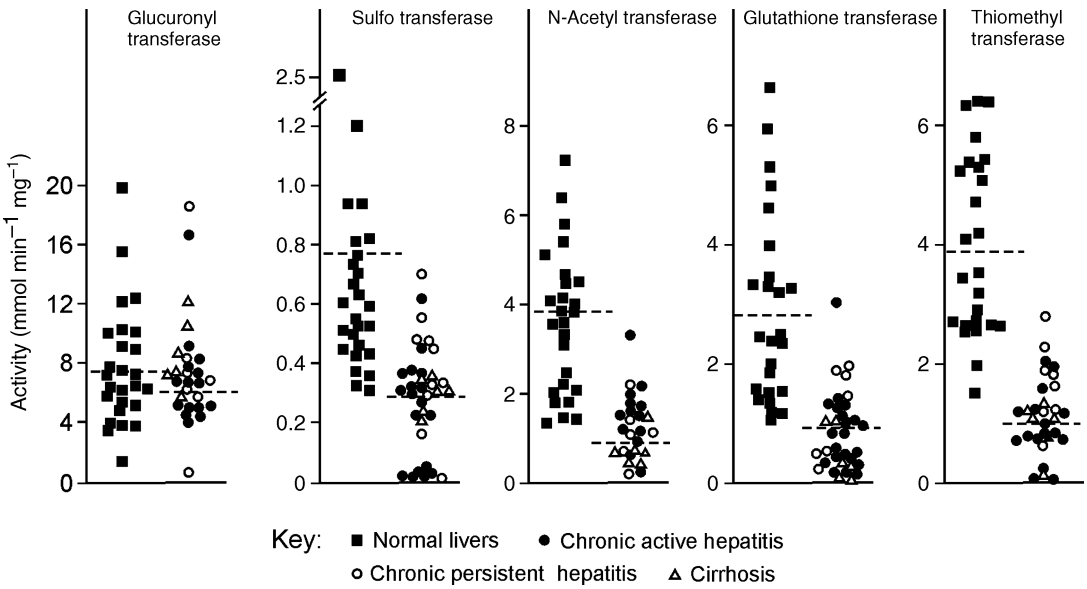

Figure 12.3 Effects of liver disease on conjugation reactions. Broken lines represent the mean value for each group. (Redrawn from Pacifici *et al.*, 1990.)

12.4.4 Examples

Table 12.2 tracks the evolution of ideas, during the early days of the study of drug metabolism in liver diseases, about how cirrhosis affects the ability of the liver to metabolize drugs. It summarizes the conclusions of a number of authors, only some of whom were able to demonstrate disease-induced changes in drug metabolism. In other studies, acute viral hepatitis caused a reduction in the rate of metabolism of hexobarbital, diazepam, pethidine and antipyrine. No change was seen in the metabolism of phenobarbital or

Table 12.2 Metabolism of a selection of drugs in hepatic cirrhosis (Curry, 1980)

Drug	Experimental observations	Comments
Pentobarbital	Overall metabolism essentially the same in cirrhotics and controls; no difference in pharmacological sensitivity	Study mainly a historical curiosity. Non-specific spectrophotometric assay; studies in first hour after i.v. dose only
Phenylbutazone	Plasma levels of drugs declined *slightly faster* in patients with advance alcoholic cirrhosis	Example of counter-intuitive result in early research; later studies showed that liver patients receive large quantities of enzyme inducing drugs that could partially offset any cirrhosis-induced decline in enzyme activity
Phenylbutazone, aminopyrine, salicylic acid, dicoumarol and antipyrine	Phenylbutazone and antipyrine had *shorter* half-life values in cirrhotics; others longer	Authors concluded that cirrhosis has little or no effect, although dicoumarol difference was substantial ($t_{1/2}$ increased by approximately 65% in cirrhosis)
Chloramphenicol	Overall metabolism essentially normal in cirrhosis	Further example of counter-intuitive result
Ethanol	Rates of metabolism: controls $98\ mg\ kg^{-1}\ h^{-1}$ and cirrhotics $102\ mg\ kg^{-1}\ h^{-1}$	Only in cirrhotics with the most advance liver disease and severe jaundice was the rate reduced
Tolbutamide	Rate of overall metabolism unchanged; rate of hydroxylation impaired	First observation of different outcome dependent on specificity of research
Digoxin	No difference in metabolism between cirrhotics and controls	Research based on urinary and faecal half-life measurements with tritiated digoxin; no excretion differences
Phenytoin	Slower metabolism in cirrhotics	Phenytoin shows saturation of the drug metabolizing enzymes within the clinical range of concentrations, thereby enhancing the probability of an effect of cirrhosis.
Thiopental	Duration of effect longer in cirrhotics	Thiopental effect controlled by redistribution between tissues; could indicate volume of distribution changes or increased brain sensitivity.
Morphine	First (?) demonstration of enhanced brain sensitivity to a centrally-acting drug	No pharmacokinetic changes
Chlorpromazine	Plasma concentrations in cirrhotics and controls similar, regardless of previous drug treatment. Electroencephalogram (EEG) different in controls and affected differently by chlorpromazine	Supports the idea that patients with liver disease are especially sensitive to centrally-acting drugs, regardless of their capacity to metabolize such compounds (see text)

(*continued*)

Table 12.2 (*Continued*)

Drug	Experimental observations	Comments
Amylobarbital	Serum concentrations in patients and controls similar, but protein binding different, and rate constants of metabolism from plasma water reduced in liver patients with low plasma albumin – no correlation with effect which was measured in early stages after i.v. injection	Supports idea that patients with certain types of liver disease do show impaired metabolism of drugs, but that compensatory changes occur in distribution compartments, leading to similar concentrations in blood
Paracetamol	Half-life in controls 2.9 ± 0.3 hours; in patients with liver damage 7.6 ± 0.8hours (both mean $\pm$ SEM)	In paracetamol overdose. May be the result of the drug damaging the liver
Suxamethonium	Close correlation between: (a) severity of liver disease and rate of hydrolysis by plasma cholinesterase; and (b) duration of apnoea	Suxamethonium is unusual among the compounds in this table, in that it is metabolized by plasma esterase and not microsomal oxidation

phenytoin, but the binding of phenytoin was reduced. The half-life of tolbutamide was shortened, and there was also an increase in the unbound concentration; it has been suggested that tolbutamide is displaced from protein by bilirubin. In cirrhosis, the half-life of phenobarbital was prolonged, with a reduction in metabolite formation, and an increase in urinary excretion of the unchanged drug. The albumin concentration was negatively correlated with the phenobarbital half-life, showing that the drug had a longer half-life when albumin concentrations were lower – probably two parallel effects. It has been suggested that the plasma albumin concentration might indicate the degree of parenchymal damage. Also in cirrhosis, lidocaine, diazepam and pethidine (meperidine) showed reduced hepatic clearance, and this was not attributable to perfusion changes, one of the proposed mechanisms.

Interestingly, in cirrhosis, phenytoin and warfarin (which has its action in the liver) show inconsistent changes. In regard to drug-induced hepatic disease, there is a significant reduction in the rate of metabolism of paracetamol, phenytoin and phenobarbital following paracetamol damage. In regard to other problems, azotemia has been shown to be associated with reduced thiopental binding. Thiopental anaesthesia is prolonged in patients with hypoalbuminaemia caused by chronic liver disease.

It is of especial interest that oral bioavailability is substantially increased in cirrhosis for drugs that have a moderate to high hepatic extraction ratio. Examples range from verapamil, with a 1.6-fold increase, to chlormethiazole, with an 11.6-fold increase, and include pethidine, morphine, nifedipine, midazolam, and most of the β-blocking drugs. It seems likely that this results from porto-caval shunting and reduced exposure to CYP3A4.

Some further examples include: (i) protein binding of sulfonamides is reduced in liver disease; (ii) (+)-tubocurarine is normally bound to plasma globulins, and resistance to this drug in hypergammaglobulinaemia due to liver disease has been attributed to increased protein binding; (iii) in liver biopsy samples, the P-450 content and *N*-demethylase activity has been shown to be normal in 'mild to moderate' hepatitis, dropping by 50% in 'severe' hepatitis and cirrhosis, with no changes in reduced nicotinamide adenine dinucleotide phosphate (NADPH) cytochrome C reductase; (iv) the hepatotoxicity of paracetamol is greater in patients treated with enzyme inducing agents; (v) there is decreased conjugation of salicylate with glycine in liver disease; (vi) hydrolysis of procaine and aspirin is slowed in patients with liver disease; (vii) propranolol has shown decreased systemic clearance, with a fall in serum albumin and rise in bilirubin, and (interestingly) prolongation of prothrombin index, but the reduction in protein binding which also

occurred supposedly did not relate to changes in proteins – there was an increase in volume of distribution, and changes in liver blood flow and plasma protein pool size seemed critical in the overall changes; (viii) alcohol dehydrogenase, and catalase are lower in patients with liver disease, but NADPH-dependent ethanol oxidizing systems are higher.

Many of the observations discussed in this section above were made before the discovery of the different isoforms of P-450, and their differential ability to metabolize their various substrates, including the significance of CYP3A4 in presystemic elimination. One of the mystery observations of the time was the fact that in many cases the ability of the liver to metabolize drugs seemed to be conserved until the very last stages of decompensation. More recently it has been shown that the different isoforms are conserved for different times (Figure 12.4). CYP2C19 activity is lost early in the process of decay of liver function, while CYP2E1 is conserved until the hepatorenal syndrome is established. CYP2D6, which is responsible for a relatively high proportion of drug metabolism, is conserved for a relatively long time, and CYP1A2 is in-between CYP2D6 and CYP2E1. Unfortunately, these data are not comprehensive, and, in particular, do not include CYP3A4. However, substrates for the CYP3A family of isoforms, such as nifedipine and midazolam, show impaired metabolism in cirrhosis.

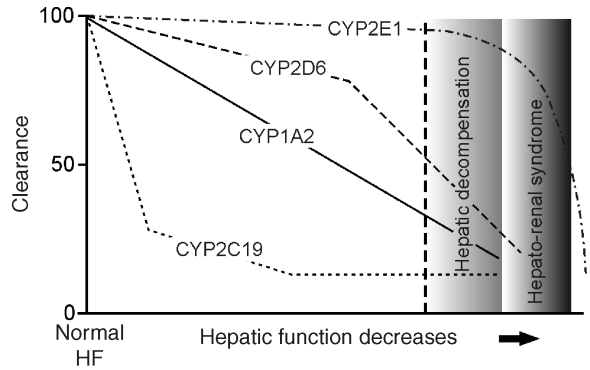

Figure 12.4 Sequential progressive model of hepatic dysfunction: implications for clearance of drugs predominantly metabolized by individual CYP pathways in liver. (Redrawn from Frye *et al.*, 2006.)

Suxamethonium (succinylcholine) is of especial interest. It is metabolized by pseudocholinesterase enzymes, which are synthesized in the liver. However, the metabolism of suxamethonium occurs in plasma, to which the enzyme migrates after it is synthesized. Furthermore, this hydrolysis reaction can be reproduced *in vitro*. Figure 12.5 shows the metabolism of suxamethonium *in vitro* by pseudocholinesterase enzymes from the plasma of patients with impaired hepatic function, including impaired synthesis of plasma pseudocholinesterase enzymes.

12.4.5 Drug effects

Studies of pharmacodynamics in relation to liver disorders have been mostly limited to β-blocking drugs, diuretics, and drugs that depress the CNS. However, topotecan is an example of an experimental anticancer drug that shows a lack of a difference between percent decrease in absolute neutrophil count (ANC) and percent decrease in platelet count as a function of the *AUC* of total topotecan during an initial course of therapy in cancer (malignant solid tumours) patients with and without impaired hepatic function. Quite apart

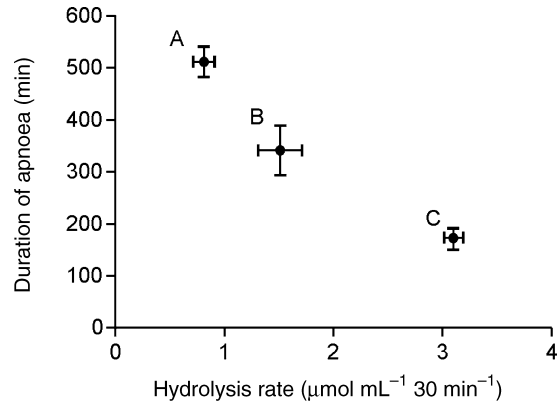

Figure 12.5 Relationship between enzymatic hydrolysis of suxamethonium and duration of apnoea after 0.6 mg kg^{-1} in patients with severe (A), moderate (B) liver disease and normal livers (C). Data are mean ± SEM. (After Birch *et al.*, 1956, and Foldes *et al.*, 1956.)

from the fact that this study showed attention to liver function in the field of cancer, this study has special interest in that the data were studied using scatter diagrams and E_{max} models of the pharmacokinetic/pharmacodynamic relationships (Figure 12.6).

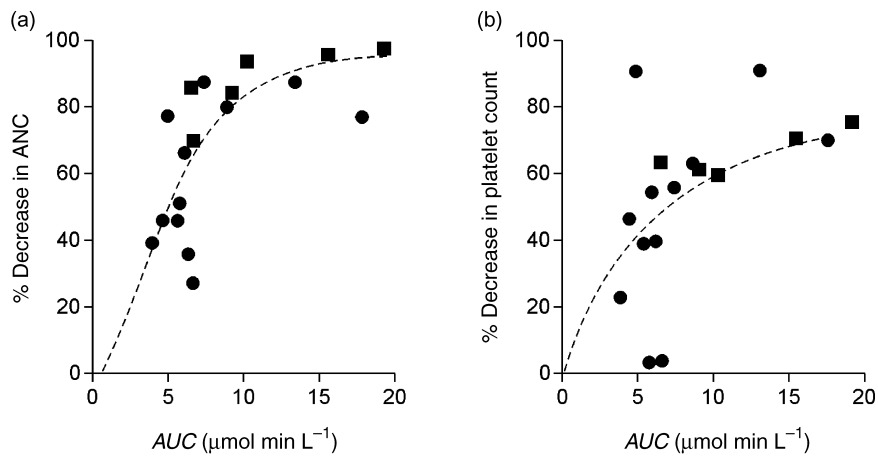

Figure 12.6 The effect of topotecan on (a) neutrophil count (ANC) and (b) platelet count as a function of *AUC*. Patients with and without liver dysfunction are represented by solid circles and solid squares respectively. (After O'Reilly *et al.*, 1996.)

In regard to β-blocking drugs it has been proposed that a decreased therapeutic effect should be expected because there is a decrease in the sensitivity to the chronotropic effects of isoprenaline in liver disease, as well as a reduction in β-adrenoceptor density in mononuclear cells. Such a decrease in effect has been observed with propranolol.

Diuretics such as frusemide (furosemide), and also triamterene, torasemide and bumetamide, also show decreased effects in liver patients, characterized by a need for a relatively high concentration of the diuretic in the renal tubules in order to induce an effect. This could be caused by a reduction in the number of nephrons

and by the maximum response per nephron, in the kidney of course, but consequent on the liver disease. However, this is likely to be offset by reduced hepatic clearance leading to higher concentrations of the drug in the kidneys, so that the effect is maintained but with a different pharmacodynamic/pharmacokinetic relationship.

As regards CNS drugs, at one time it was rare that drug responses were adequately measured in patients with hepatic problems, even though such patients are particularly sensitive to CNS drugs. A study with chlorpromazine highlighted this. The interest in chlorpromazine lay in the fact that, in spite of the similarity in the plasma levels, significant differences between patients and controls, in the encephalogram (EEG) and in the drug effects on the EEG, were noted. This confirmed the widespread suspicion that patients with liver disease are unusually sensitive to behavioural effects of drugs with central actions, quite apart from any differences in drug metabolism.

An interesting study of the effect of liver disease on plasma levels of another centrally-acting drug, amylobarbital, has been reported (Mawer *et al*., 1972). Two groups of liver patients and a control group of healthy subjects were given single doses of amylobarbital by intravenous injection. Plasma levels of the drug were similar in all three groups, but the degree of protein binding of amylobarbital was reduced in one of the two groups of patients. The members of this group were characterized by their abnormally low concentrations of albumin in serum. So with lower protein binding and the same total drug concentrations in serum, concentrations in serum water were obviously higher this group, and, furthermore the half-life of the terminal phase was longer. Both groups of patients showed an increase in the rate constant of the faster (redistribution) phase of the double exponential graph of concentration against time. The slower phase is an indication of the combined rates of metabolism and excretion, probably influenced, at least in part, by the rate of return of the drug from tissues. The faster phase is an indication of tissue penetration by the drug.

It thus appears that there may in fact be a reduction in the capacity of the diseased liver to metabolize amylobarbital, but only in those patients who have reduced concentrations of albumin, which is considered to be a parallel but independent consequence of reduced hepatic function. However, it appears that the body at least partially compensates this impaired function, by modifications in the rate and extent of drug penetration into tissues. In the end, similar total concentrations in plasma result. Finally, in this amylobarbital study, the clinical response to amylobarbital was similar in the three groups. However, it was assessed at the early time points when there were no major drug concentration differences between the two groups. These differences were most dramatic at later time points, when the effect had largely worn off. Thus the extreme complexity of the relationship between liver disease and drug metabolism is emphasized.

The examples of Table 12.2 demonstrate the development of knowledge in this context from counterintuitive early results to detailed understanding.

12.5 Renal impairment

12.5.1 General considerations

Kidney failure can be acute, with rapid decline in function but equally rapid recovery if the pathology is reversed, or chronic with slow progression and little chance of recovery. In either case there is accumulation of metabolic waste products in the blood (azotaemia or uraemia) especially urea and creatinine, plus the potential for anaemia, acidosis, decreases in blood calcium and vitamin D, and increases in blood phosphate, parathyroid hormone, and potassium. Acute kidney failure can be caused by impairment of the blood supply to the kidney (e.g. congestive heart failure, bleeding, dehydration, shock, or liver failure – hepatorenal syndrome) or obstruction of urine flow (e.g. prostate enlargement or other tumours) or injury (e.g. allergic reactions within the kidney, toxic chemicals, conditions affecting glomerular filtration, blocked blood

vessels or crystal deposits). Chronic kidney failure can result from high blood pressure, urinary tract obstruction, glomerulonephritis, structural abnormalities, diabetes, or autoimmune disorders. Kidney function is typically evaluated by means of creatinine clearance, which is considered elsewhere (Section 3.2.1.4). Creatinine is freely diffusible at the glomerulus, and there is approximately equal transfer in each direction across the renal tubule, so creatinine clearance effectively measures glomerular filtration rate (GFR). Shortcuts based on measurement of serum creatinine tend to underestimate creatinine clearance, although they do provide a useful clinical tool.

The claim that kidney disease reduces the rate of elimination of drugs cannot be challenged. However, it should be realized that drugs may be excreted unchanged to any extent, varying from 0 to 100%. Clearly, a drug that is 100% dependent on the kidney for its removal from the body might be greatly affected by kidney disease. In contrast, a drug that is not excreted unmetabolized is less likely to be affected. However, the excretion of the metabolites of this type of drug, as opposed to the excretion of the unchanged drug, will almost certainly be affected. The metabolites will accumulate in plasma, leading to an exaggerated response if the metabolites contribute to the pharmacological effect or, possibly toxicity, that is not seen when the metabolites are excreted normally. If the presence of large quantities of metabolites reduce the rate of metabolism of the unchanged drug, by metabolite inhibition, then there is the theoretical possibility of accumulation of unmetabolized drug. Additionally, renal impairment is likely to lead to varying degrees of water loading and this may lead to modification of the concentrations of the drug in the fluid compartments of the body, including plasma.

12.5.2 Mathematical approach

The pharmacokinetic significance of changes in GFR is conveniently considered from a worked example for digoxin. The rate constant of elimination (k) is given by:

$$k = k_{\mathrm{R}} + k_{\mathrm{NR}} \tag{12.2}$$

where k_{R} is the rate constant of renal elimination and k_{NR} is the rate constant of non-renal elimination (hepatic and other metabolism and miscellaneous non-renal processes), and k_{R} is proportional to creatinine clearance, CL_{cr}.

The normal half-life of digoxin is 1.7 days, and digoxin is eliminated ~65% unchanged in the urine, so Equation 12.2 becomes:

$$k = 0.65k + 0.35k \tag{12.3}$$

and because $t_{1/2} = 0.693/k$ (Equation 1.10), then $k = 0.408\ \mathrm{d}^{-1}$, from which k_{R} and k_{NR} are 0.265 and $0.143\ \mathrm{d}^{-1}$, respectively. The value of k_{R} applies when GFR is 'normal', i.e. $125\ \mathrm{mL\ min}^{-1}$. We can calculate the half-life for partial renal failure represented by, say a CL_{cr} of $50\ \mathrm{mL\ min}^{-1}$. Thus, as k_{R} is proportional to CL_{cr}, the 'new' k_{R} is:

$$k_R = \frac{50}{125}0.265 = 0.106\ \mathrm{d}^{-1}$$

As there is no reason, in this example, to suppose that k_{NR} has changed, the value of the elimination rate constant when $CL_{\mathrm{cr}} = 50\ \mathrm{mL\ min}^{-1}$, is $0.106 + 0.143 = 0.249\ \mathrm{d}^{-1}$. Solving for half-life in this state, $t_{1/2} = 2.78$ d. Thus, the half-life is not proportional to creatinine clearance. In this example, a 60% reduction in GFR will lead to a 65% increase in half-life. For a shortcut, nomograms exist for clinical dose adjustment based on serum creatinine.

In older literature, a more general approach to this is to be found, using the equation:

$$k = k_{NR} + \alpha CL_{cr} \tag{12.4}$$

where α is a factor of proportionality expressing the relation between the renal elimination rate of the drug and CL_{cr}. According to this equation, for any drug, a graph of k versus CL_{cr} will be one of:

- A straight line through the origin if the drug is entirely eliminated by the kidneys ($k_{NR} = 0$; $\alpha > 0$).
- A line parallel with the x-axis and intercepting the y-axis if the drug is entirely eliminated extrarenally ($k_{NR} > 0$; $\alpha = 0$).
- A straight line intercepting the y-axis if both routes of elimination are involved ($k_{NR} > 0$; $\alpha > 0$).

Gabapentin is an example of a drug that would show the characteristics of the first of these cases. A limited number of highly lipophilic drugs, such as the tricyclic antidepressants virtually meet the specification for the second case. Digoxin is in the third category.

More modern literature favours a direct analogue of the equations above for the situation in which drug clearance data are available, rather than rate constants or half-life values. Thus:

$$CL_{ur} = CL_{NR} + CL_R \frac{CL_{cr(ur)}}{CL_{cr(N)}} \tag{12.5}$$

Where CL_{ur} is the systemic clearance of the drug in the uraemic patient (subscript ur) and N stands for 'normal.' This follows from the additivity of clearance, the use of creatinine clearance as the indicator of renal function, and the fact that renal clearance of the drug is proportional to creatinine clearance. It also assumes that there is no effect of renal impairment on non-renal elimination of the drug (see later). Thus, if the ratio of the two creatinine clearances is known, along with the drug clearances for normal subjects, the clearance in the uraemic patient can be calculated. Alternatively, if the normal total body clearance and f_e, the fraction excreted unchanged in the normal case, are known, then:

$$CL_{ur} = CL(1-f_e) + f_e CL \frac{CL_{cr(ur)}}{CL_{cr(N)}} \tag{12.6}$$

Equation 12.6 is for systemic drug clearance in the patient with partial renal impairment, in terms of systemic clearance (CL) in a 'normal' person (no impairment) adjusted for the fraction excreted by non-renal processes plus CL adjusted for the fraction excreted unchanged by the kidney multiplied by the ratio of the relevant creatinine clearances. A further useful relationship is then possible, by dividing Equation 12.6 by CL:

$$\frac{CL_{ur}}{CL} = (1-f_e) + f_e \frac{CL_{cr(ur)}}{CL_{cr(N)}} \tag{12.7}$$

12.5.3 Examples

In practice, the presence of renal impairment is a reason for care with any drug, but plasma level studies have been largely concerned with drugs excreted mostly unmetabolized. The majority of the work has concerned antibiotics, and a selection of values of the rate constants of elimination in anuric patients and in patients with normal kidney function is shown in Table 12.3. The first four columns show the parameters for normal subjects (N) while the last two columns are the elimination rate constant, $k_{(anuric)}$ and half-life, $t_{1/2(anuric)}$, respectively, in anuric patients. Of course, there is no equivalent column for apparent first-order rate constants for renal excretion, $k_{R(anuric)}$, as these patients were not producing urine. These data were mostly compiled from databases such as that in *Goodman and Gilman's the Pharmacological Basis of Therapeutics*, but data in anuric patients is from Dettli *et al*. (1974).

Table 12.3 Pharmacokinetic data relevant to drug elimination in anuric patients and patients with normal function

Drug	f_e	$t_{1/2(N)}$ (h)	$k_{(N)}$ (h^{-1})	$k_{R(N)}$ (h^{-1})	$k_{(anuric)}$ (h^{-1})	$t_{1/2(anuric)}$ (h)
Desipramine	0.02	22.0	0.032	0.0006	ND[a]	ND
Cefaloridine	0.059	1.36	0.51	0.03	0.03	23.1
Erythromycin	0.13	1.6	0.43	0.056	0.13	5.33
Sulfamethoxazole	0.14	9.8	0.071	0.0099	0.07	9.9
Chloramphenicol	0.15	3.3	0.21	0.032	0.2	3.47
Tetracycline	0.58	10.6	0.065	0.038	0.008	86.6
Digoxin	0.65	41.0	0.017	0.011	0.008	86.6
Gabapentin	1.0	6.5	0.11	0.11	0.0053	132.0

[a] Not determined. Note that in the symbols in this table, as in the text, N indicates normal, and R indicates renal.

Desipramine is included as an example with virtually no excretion of the parent drug, and for which it can be presumed that renal failure would have no effect on the half-life, while gabapentin is at the other extreme, and would presumably not be eliminated at all in an anuric patient. Digoxin is the outstanding example of a clinical need to adjust dosage in renal failure. Five of the compounds are antimicrobial drugs. One of them, chloramphenicol, is partly dependent on metabolism and excretion in bile for its removal from the body. Sulfamethoxazole is a sulfonamide; it also undergoes metabolism. These two compounds showed quite small changes in their overall kinetics, even though about one-sixth excreted in the unchanged form by the kidney – they were apparently the least affected of the seven compounds. Erythromycin, with a percentage excretion unchanged similar to that of sulfamethoxazole and chloramphenicol showed a three-fold increase in half-life, but cefaloridine, with a very small percentage excretion unchanged, showed a dramatic increase in half-life. It should be noted that the data in Table 12.3 were taken from a vast amount of data available on the relationship between renal failure and drug elimination for individual examples, for the purpose of illustrating possibilities. Data of this type are available for approximately 150 drugs, with heavy emphasis on antiinfective agents. Tabulations of this data are to be found in texts concerned principally with patient care. Generally speaking this database shows a greater impact of renal failure on drugs with the higher levels of elimination through the kidney. It is now standard clinical practice to base drug dosage with some of these compounds on creatinine clearance.

It has been suggested that various other differences arise as the result of renal failure. For example, there is apparently decreased absorption of oral iron, a carrier-mediated process, and it has also been suggested that nitrofurantoin shows impaired absorption, as there is no build-up in plasma although urinary excretion is reduced. It is probable that a compensating increase in hepatic elimination explains this. This is of considerable interest, as renal and hepatic impairment can occur together, or can compensate for each other.

There is evidence of protein binding changes in renal failure. Binding of sulfonamides is reduced in nephrectomized patients. Phenytoin binding is also reduced, but binding of basic drugs, such as desipramine, quinidine, dapsone and diazoxide is unchanged. In the case of diazoxide, this causes an increased hypotensive effect. Metabolism may be affected by renal failure. This has been shown by studies with isoniazid, sulfisoxazole, hydralazine (all acetylated), procainamide (the hydrolysis reaction, although both acetylation and hydrolysis occur) and hydrocortisone (reduction). Renal failure can also change receptor sensitivity because of its influence on electrolyte and acid-base balance.

Increased hepatic elimination has been presumed for amylobarbital, phenytoin and propranolol in patients in renal failure, on the basis of reduced renal clearance without corresponding changes in overall pharmacokinetic properties. Pindolol, normally 40% excreted unchanged shows decreased renal excretion but no half-life change (and no protein binding change). Something similar occurs with cefaloridine. The hydroxylated metabolites of barbiturates, normally considered inactive, achieve importance in uraemia, probably because of changes in end organ sensitivity plus their accumulation to high concentrations. The half-life of sotalol is 5 h in normal subjects, 42 h in renal patients, and 7 h in the same patients on dialysis. It is not bound to plasma protein.

Tissue distribution may be affected. For example, the distribution of ampicillin within the kidneys of patients with chronic glomerulonephritis is different from that of control subjects, and there will be clearly be difficulty in achieving therapeutic levels of drugs when the kidney is the target organ. Interestingly, it has been shown that the distribution of kanamycin is unaffected by renal failure, and this has been attributed to lack of protein binding of this drug.

There are some methodological problems especially relevant to renal failure and hepatic problems. First, drugs are eliminated at rates and to extents. One can change or both can change. Rates of renal and hepatic elimination are interrelated only by biological factors, but the two extents, summed, can only equal the dose. Studies which fail to take this into account can be quite misleading. Second, half-life is directly proportional to volume of distribution and inversely proportional to whole body clearance (Equation 4.7) All three parameters are derived from one set of data, a series of plasma concentration measurements. Researchers who think that a change in one necessarily means no change in the others are in danger of missing the vital implications of data.

12.6 Thyroid disease

12.6.1 General considerations

The thyroid gland is driven by the pituitary, which secretes thyroid stimulating hormone (TSH). The thyroid gland can be overactive (hyperthyroidism, or thyrotoxicosis, including Grave's disease), or underactive (hypothyroidism), or its control by TSH can be abnormal. The normal gland is described as euthyroid. The thyroid is particularly susceptible to cancer, inflammation (thyroiditis), and lack of, or overload with, dietary iodine (e.g. Derbyshire neck) or drug-derived iodine (e.g. from amiodarone). The gland secretes tetraiodothyronine (L-thyroxine, T4) which is deiodinated to triiodothyronine (T3). Administration of L-thyroxine as a therapeutic agent can be to restore missing normal hormone (restoring the euthyroid condition in hypothyroidism), or it can be to suppress endogenous thyroxine production (restoring the euthyroid condition in hyperthyroidism), by means of a feed-back mechanism that suppresses TSH production.

Hyperthyroidism can result in an increased rate of gastric emptying, reduction in intestinal transit time, increased cardiac output and blood flow to tissues such as the liver and kidney, increased activity of hepatic microsomal enzymes and therefore hepatic intrinsic clearance, an increase in glomerular filtration rate, and reduced concentrations of albumin and α_1-acid glycoprotein in plasma. Hypothyroidism, generally speaking, does the opposite. All of these changes have the potential to alter drug disposition. Also, their reversal by means of effective therapy makes possible the longitudinal study of patients in both impaired and euthyroid states.

12.6.2 Examples

There are numerous examples of compounds and their pharmacokinetic properties that illustrate the general principles implicit in the previous two paragraphs. For example, in hyperthyroidism, the absorption rate of riboflavin and paracetamol is increased, and the rate of oxidative metabolism of tolbutamide, theophylline, antipyrine and metoprolol is increased. The rate of glucuronidation of oxazepam is increased, the renal clearance of digoxin is increased, and the plasma protein binding of propranolol and warfarin is decreased. Conversely, in hypothyroidism, the rate of absorption of paracetamol is decreased, the rate of oxidative metabolism of antipyrine is decreased, the renal clearance of digoxin is decreased, and the plasma protein binding of propranolol is increased. However, in hypothyroidism, opposite effects of hyperthyroidism do not *necessarily* occur, as with riboflavin absorption, oxazepam glucuronidation, and warfarin binding, and, in some cases (e.g. phenytoin and diazepam metabolism) there are no effects in either direction, and/or data are conflicting, or just not available. Three well-investigated cases, of digoxin, propranolol and warfarin, are worthy of further attention.

Digoxin bioavailability is especially affected by intestinal P-gp expression. This has been measured by means of reverse transcriptase-polymerase chain reaction of MDR1 messenger ribonucleic acid (mRNA) and immunohistochemical examination, in healthy volunteers before and after suppression of TSH with

L-thyroxine. To complement this, the pharmacokinetics of the P-gp substrate talinolol were assessed after i.v. and oral administration. L-thyroxine increased duodenal MDRI mRNA expression, and P-gp, 1.4-fold and 3.8-fold respectively – there were minor changes in talinolol half-life and *AUC*, consistent with reduced systemic availability of the oral doses under the influence of the L-thyroxine.

This work is relevant to the case of digoxin, with which relatively high doses of the drug are needed to control the heart rate of patients with hyperthyroidism and atrial fibrillation, not particularly because of any changes in absorption *per se*, volume of distribution, biliary clearance, renal clearance, or non-renal clearance (although some changes have been observed), but because of the induction of P-gp leading to increased efflux of digoxin from the duodenal tissue against the flow of absorption, reducing the proportion of the dose reaching the general circulation.

Warfarin requirements are increased in hypothyroidism but reduced in thyrotoxicosis. In part, the effect of warfarin on the regeneration of reduced vitamin K, an essential cofactor in the activation of clotting factors II, VII, IX and X by post-translational carboxylation of glutamate residues leads to diminished synthesis of active coagulation factors and accumulation of their non-functional precursors, and thus thyrotoxic patients exhibit an increase in prothrombin time. Although there are some reports of changes in the half-life of warfarin and in its binding, in total it is obvious that there are no dramatic changes in pharmacokinetic parameters of warfarin of sufficient magnitude to be associated with this, so the warfarin potentiation is thought to reflect an enhanced pharmacodynamic effect. Steady-state plasma concentrations of the coagulation factors are decreased, because of an enhanced degradation rate in thyrotoxicosis, and shorter plasma half-life values of the coagulation factors. The opposite is observed in hypothyroid states.

Propranolol clearance after intravenous injections is increased by approximately 50% in the hyperthyroid state, an effect attributed to increased liver blood flow. However, there is also increased clearance after oral dosing that is attributed to increased hepatic microsomal intrinsic clearance. There is also a slight reduction in protein binding. These changes result in a reduction in serum triiodothyronine concentrations, leading to the idea that propranolol is a useful treatment for certain hyperthyroid conditions, such as short-lived excessive secretion of thyroid hormone, which occurs in 'thyroid storm'. This occurs by virtue of propranolol inhibiting the sympathetic drive caused by thyroid hormone. Therefore it inhibits its own enhanced clearance. Simultaneous determination of intravenously and orally administered propranolol in hyperthyroid and euthyroid patients has shown markedly higher plasma concentrations of the drug following the oral doses, with smaller increases following the i.v. doses, and no differences in half-life, indicating increased clearance in the hyperthyroid state, but to an added degree with oral dosing, raising the question of whether CYP3A4 is particularly affected in the hyperthyroid state (Figure 12.7).

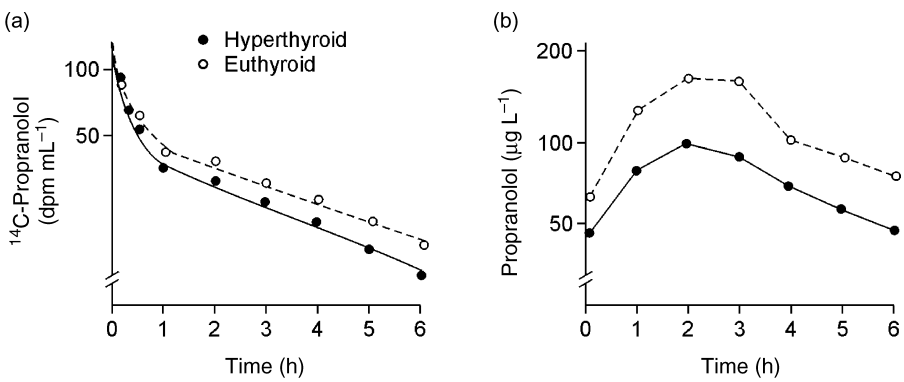

Figure 12.7 Simultaneous determination of i.v. (a) and oral (b) kinetics of propranolol in patients when hyperthyroid and euthyroid.

Specific information regarding the effect of thyroid function on individual drug-metabolizing isoforms of CYP 450 seems to be unavailable. However, in one particular study, the addition of triiodothyronine to primary hepatocytes significantly *reduced* CYP3A4 protein and mRNA, and, conversely, experimental hypothyroidism in rats led to CYP3A4 induction and CYP2C11 suppression. Thyroidectomized rats exhibited a marked increase in CYP8B1 protein and mRNA levels, whereas treatment of normal rats with L-thyroxine significantly reduced CYP8B1 activity and mRNA. No human studies appear to have been conducted as yet with substrates for specific isoforms, so the propranolol data remains the only basis at present for an expectation of enhanced presystemic metabolism of drugs by CYP3A4 in the hyperthyroid state (Sarlis and Gourgiotis, 2005).

12.7 Summary

A vast amount of knowledge exists on the effect of diseases on the pharmacokinetic and pharmacodynamic properties of drugs. Much of this knowledge consists of isolated pieces of information about single examples, and the search for themes of broader application can be arduous. With respect to diseases that effect drug disposition, the following general principles are well established:

- Experimental difficulties involved in separating disease effects from other factors pose difficult problems when seeking general principles.
- Gastrointestinal disorders can modify both the rate and extent of absorption, with increases or decreases dependent on the interplay of pH, gastric motility, surface area available for absorption, and other pathological changes, and on the chemical and biochemical properties of the particular drug, permitting a logical prediction of the effect on the basis of general principles.
- CHF leads to changes in drug absorption, hepatic and renal blood flow, hepatic intrinsic clearance, and presystemic elimination, mostly reductions in rate, and the effect on any particular drug will depend on which processes are predominant. It is not easy to separate the effects of oedema from those of the disease.
- Hepatic disorders reduce blood flow, hepatic intrinsic clearance, and plasma protein binding, but the consequences of these effects are modified in many cases by late onset, for multiple reasons including compensatory enzyme induction. Clearance calculations provide useful approaches to quantifying these effects. The significance for any particular drug will depend on the interplay and predominance of the various factors in its disposition. Centrally acting drugs show enhanced pharmacodynamic effects.
- Renal disease can cause reduced glomerular filtration and modified renal tubular transport. These changes mainly affect drugs dependent on urinary excretion of the unmetabolized drug, and this can be especially important in the dosing of digoxin, with its narrow margin if safety, and a whole range of antibiotics. Clearance calculations facilitate safe dosing of these drugs. There is a considerable incidence of concomitant occurrence of hepatic disease in renal disease patients.
- With exceptions, hyperthyroidism leads to enhanced rates of the drug disposition processes and hypothyroidism to the opposite.

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