Liver disease has a profound and unpredictable effect on drug kinetics. Unfortunately, there are relatively few detailed studies of antimicrobials and the majority of illustrations of general principles are drawn from other drug classes. It must be emphasized at the outset that alteration in pharmacokinetics is not a major cause of toxicity with these agents and that the most serious adverse reactions to drugs in patients with liver disease are due to precipitation of coma by sedatives, by drugs that affect salt and water homoeostasis and by drugs that cause gastrointestinal haemorrhage.

The mechanisms for increased adverse drug reactions in patients with liver disease are not always clear (Secor & Schenker, 1987). For example, nephrotoxicity from aminoglycosides appears to be potentiated by liver disease although they are excreted almost entirely by renal processes (Cabrera et al., 1982; Moore, Smith & Lietman, 1986). It is important to consider wherever possible the pharmacodynamic properties of drugs in liver disease and not just the alteration in pharmacokinetics.

Liver disease can influence pharmacokinetics by alteration of intrinsic hepatic clearance, by reduction in metabolic capacity or bypassing of the liver by portal-systemic vascular shunting, by reduction in the concentration of drug binding proteins in serum, by changing the affinity of drug binding proteins and by altering drug absorption from the gastrointestinal tract. These processes have been recently reviewed in detail (Secor & Schenker, 1987). In general the liver has a considerable capacity to metabolize drugs, which is only significantly impaired by severe liver disease. However, altered pharmacokinetics have been reported in acute hepatitis because of alteration in protein binding (Williams et al., 1977). In addition, the distribution of a disease process within the hepatic lobule is important because the majority of drug metabolizing reactions are carried out in the smooth endoplasmic reticulum, which is located pericentrally in the hepatic lobule. Impairment of drug metabolism has been reported without gross deterioration in general liver function in acute viral hepatitis and alcoholic hepatitis, which predominantly affect the pericentral area. In contrast, primary biliary cirrhosis initially affects the periportal region and drug metabolism is not impaired until the terminal phase of the disease (Secor & Schenker, 1987).

There are two distinct components to hepatic drug metabolism. Phase I metabolism involves the metabolic degradation of a drug by oxidation, reduction or hydrolysis, while phase II metabolism involves the conjugation of a drug, or of its metabolite, chiefly by acetylation, glucuronidation, sulphation or mercapturic acid synthesis.

Of the phase I reactions, by far the most important are the oxidation steps carried out by the mixed function oxidases, a group of enzymes principally associated with the endoplasmic reticulum of liver parenchymal cells. The oxidative system involves an electron transport chain with cytochrome P450, a haem protein, as the terminal component, which in its reduced form complexes with many drugs to facilitate their oxidation. It exists in several isoenzymic forms each of which appears to be responsible for a number of oxidative processes. The potential for substrate specificity of cytochrome P-450 is illustrated by the following drug interaction study involving two known inhibitors of drug oxidation in normal volunteers. Sulphonaphenazole significantly decreased the clearance of tolbutamide (0.08 vs. 0.26 ml/min/kg) but had no effect on the clearance of antipyrine. In contrast, primaquine reduced the clearance of antipyrine (0.38 vs. 0.63 ml/min/kg) but had no effect on the clearance of tolbutamide. It was concluded that sulphonaphenazone and primaquine selectively inhibited different forms of cytochrome P-450 in man (Back et al., 1987). Drugs may be metabolized by either phase I or phase II reactions, or by both. In general, phase II metabolism results in the formation of polar, biologically inactive...
metabolites which because of their polarity are excreted in the bile or in the urine. In contrast, although phase I metabolism may inactivate the drug (e.g. oxidation of phenytoin), it may also augment the pharmacological effect of the parent drug, either by yielding a metabolite with greater activity than the parent drug (e.g. conversion of chloral hydrate to trichloroethanol) or a metabolite with lower intrinsic activity than the parent drug but a greatly increased half life (e.g. conversion of diazepam to desmethyldiazepam). Finally, phase I metabolites that do not retain the pharmacological activity of the parent drug may be toxic (Park & Kitteringham, 1987). Very rarely, phase II metabolites are toxic (e.g. acetyl isoniazid is a potentially hepatotoxic conjugate of isoniazid).

Apart from the intrinsic ability of hepatocytes to metabolize a drug, hepatic drug clearance is determined by hepatic blood flow and by the fraction of a drug which is unbound to serum proteins. On theoretical grounds, drugs can be divided into broad groups. 'Flow limited' or 'high clearance' drugs (e.g. ketoconazole, miconazole) are cleared avidly by the liver; their clearance is only limited by hepatic blood flow and should be little affected by changes in hepatocyte function or protein binding. In contrast, for 'capacity limited' or 'low clearance' drugs (e.g. ampicillin, clindamycin) hepatic metabolism is already maximal and their clearance should be sensitive to small changes in protein binding or hepatocyte function. In practice, disease of the hepatocytes can impair the clearance of both types of drugs and, as yet, these theoretical concepts have little practical clinical application. For a full discussion of current theory see Pond & Tozer (1984).

First-pass metabolism refers to the extensive hepatic extraction of an orally administered drug before the drug has reached the systemic circulation. An extreme example is rifampycin which was undetectable in the serum of normal subjects after oral dosing, whereas up to 7 mg/l was measured in the serum of patients with cirrhosis (Acocella et al., 1972). Because of this phenomenon (Pond & Tozer, 1984) and because of the effect of liver disease on drug absorption (Secor & Schenker, 1987), pharmacokinetics of orally administered drugs are likely to be particularly unpredictable in liver disease. An increase in the systemic availability (area under the plasma drug concentration versus time curve) after oral dosing of a drug that normally undergoes first-pass metabolism may be the most important effect of liver disease on pharmacokinetics.

There is conflicting evidence on the capacity for enzyme induction in patients with liver disease. Rifampicin serum concentrations decreased with chronic dosing in normal patients but increased in patients with cirrhosis, which suggested that enzyme induction had not occurred in the latter (Acocella et al., 1972). In contrast, phenylbutazone clearance was impaired in patients with cirrhosis unless they had received drugs that induce hepatic enzymes, in which case their phenylbutazone clearance was apparently normal (Levi, Sherlock & Walker, 1968).

The majority of studies of the pharmacokinetics of antibacterial drugs in liver disease have focussed on drugs that are significantly (>10%) metabolized by the liver, e.g. ampicillin (Lewis & Jusko, 1975), cefotaxime (Balant, Dayer & Auckenthaler, 1985), cephalothin (Ohashi, Tsuno & Tsuneoka, 1986), chloramphenicol (Acocella, 1983), clindamycin (Hinthorn et al., 1976), isoniazid (Acocella et al., 1972), lincomycin (Hoyumpa & Schenker, 1982), metronidazole (Farrell et al., 1984), mezlocillin (Bunke et al., 1983), nafcillin (Marshall et al., 1977) and rifampicin (Acocella et al., 1972). However, although there are relatively few studies it is clear that liver disease also affects the pharmacokinetics of drugs that are not significantly metabolized, e.g. carbenicillin (Hoyumpa & Schenker, 1982), cefazolin (Ohashi et al., 1986) and vancomycin (Brown et al., 1983). Ohashi et al. (1986) included protein binding data and were able to show that increased clearance of cefazolin in patients with cirrhosis was due to a fall in protein binding from 89% to 72% and consequent increased renal clearance. The majority of these effects are not significant; those that are of proven or potential significance are summarized in Table I.

There are two methodological problems which make it difficult to draw general conclusions from published studies. The first is that there is no adequate means of defining liver function for patients with 'liver disease'. The available evidence suggests that patients with any given type of pathology form a very heterogeneous group, and this variation is an addition to the marked differences between diseases caused by their variable distribution within the hepatic lobule (Secor & Schenker, 1987). For example, clindamycin clearance was impaired by cirrhosis but not by acute or chronic hepatitis (Hinthorn et al., 1976), whereas rifampicin clearance was impaired by acute hepatitis and cirrhosis (Meinz & von...
Table I. Specific recommendations for alteration in antimicrobial chemotherapy in liver disease

**Drugs with markedly impaired elimination in liver disease**

- Mezlocillin (Bunke et al., 1983): reduce dose by 50% in severe liver disease.
- Azlocillin and piperacillin are likely to have similar kinetics but have not been studied.
- Clindamycin and erythromycin: no specific recommendations on dosage, but use with caution.

**Drugs that are significantly cleared by the liver and are potentially toxic**

- Ketoconazole and miconazole: monitoring of serum concentrations recommended in severe cirrhosis (Secor & Schenker, 1987).
- Metronidazole: reduce dose by 50% in patients with severe cirrhosis and/or associated renal insufficiency (Secor & Schenker, 1987).
- Nitrofurantoin, chloramphenicol, sodium fusidate and pyrazinamide: no information on use in liver disease but potentially toxic; avoid if possible.
- Rifampicin: limit dose to 6-8 mg/kg in patients with severe chronic liver disease (Curci, Claar & Bergamini, 1973).
- Esters of ampicillin: potentially toxic products of hydrolysis of ester may accumulate (Anonymous, 1976).

**Drugs that may have altered pharmacodynamics in liver disease**

- Aminoglycosides: possibly enhanced nephrotoxicity (Cabrera et al., 1982; Moore et al., 1986).
- Carbencillin and ticarcillin; high sodium content, avoid if possible.
- Quinolones: no information but patients with liver disease are particularly sensitive to drugs that inhibit gamma amino butyric acid (GABA) (Fowler & Schafer, 1981).

Oldershausen, 1971). However, it is impossible to say whether these results reflect truly different effects of these disease states on the two drugs, or simply different hepatic function amongst the patients with hepatitis in the two studies. The second methodological problem is the lack of pharmacokinetic detail in most studies. The clearance of a drug from the blood (‘systemic clearance’) is not a reliable indicator of hepatocyte function. For example, although systemic clearance of naproxen was apparently unimpaired in patients with cirrhosis, the hepatic clearance was in fact reduced but this was compensated by a reduction in protein binding and consequent increase in the proportion of naproxen available for metabolism (Williams et al., 1984). Measurement of protein binding should be part of any study on the effects of liver disease on pharmacokinetics. In addition to binding of acidic drugs to albumen, it is important to consider binding of basic drugs to α1-acid glycoprotein (AAG). For example, the unbound fraction of erythromycin in plasma was 58% in patients with cirrhosis and 30% in normal subjects owing to low serum concentrations of AAG in the patients with cirrhosis. This, together with a decrease in hepatic clearance of unbound erythromycin, resulted in markedly increased plasma concentrations of unbound erythromycin in patients with cirrhosis (Barre et al., 1987). It is also vital to account for all the other variables that have a profound effect on hepatic drug metabolism (e.g. age, sex, race, inheritance, diurnal variation, nutritional status, alcohol, smoking, other drugs) (Vesell & Penno, 1983). Finally, spurious effects of liver disease on pharmacokinetics may occur because hyperbilirubinaemia interferes with photometric immunoassays; falsely low gentamicin concentrations have been reported with the TDX system in jaundiced patients (Jolley et al., 1981).

In conclusion, liver disease has complex effects on the pharmacokinetics of all drugs, including drugs that are not excreted by the liver. For this reason, and because of the danger of alterations in pharmacodynamics, all drugs should be prescribed with extreme caution to patients with liver disease. The pharmacokinetics of orally administered drugs are particularly erratic in liver disease. It is impossible to predict the pharmacokinetics of a drug from available tests of liver function or from the pharmacokinetics of other drugs. Even studies of the same drug in other patients with liver disease are of limited value, because of the difficulty in defining the precise changes in hepatic function which are present in an individual patient. For this reason pharmacokinetic studies of new antimicrobials in patients with 'liver disease' are of doubtful practical value, although they may yield results of theoretical interest, provided that measurements of protein binding are included and that patients are well matched for other variables that affect hepatic drug metabolism.

**Acknowledgement.** I am grateful to Professor I. H. Stevenson for his help with this article.

P. G. DAVEY,
Ninewells Hospital,
Dundee DD1 9SY, UK
References

References in the text


In addition to the cited references, the following are recommended for a more detailed account of general principles.

Leading articles


The effect of renal failure on the pharmacokinetics of antibiotics

The concentrations of an antibiotic in the body depend partly on the relative rates of its input and elimination. The latter may be expressed by the overall elimination rate constant, \( k_a \), which is the fraction of antibiotic in the body removed as a function of time. Many antibiotics are largely removed from the body by the kidneys while others are excreted by non-renal routes, so the overall elimination rate constant \( k_e \) can be thought of as the addition of two lesser rate constants, those of renal and non-renal elimination, \( k_{ar} \) and \( k_{nr} \), respectively. The latter is often termed \( k_m \) the rate constant for metabolic elimination, but strictly speaking there may be extra-renal elimination apart from that by metabolism, such as the excretion of intact drug in the bile. Thus:

\[
 k_e = k_{ar} + k_{nr}.
\]

Clearly, when in the normal subject \( k_e \) greatly exceeds \( k_{nr} \) most of the antibiotic will be eliminated unchanged via the kidneys in the urine, and loss of renal function will have a profound effect on \( k_e \). When most of the antibiotic is eliminated by non-renal mechanisms, and \( k_{nr} \) greatly exceeds \( k_{ar} \), renal failure will have little or no effect on the \( k_e \) of the parent antibiotic. Metabolites of antibiotics, which are themselves products of non-renal elimination, may nevertheless depend on renal excretion for their elimination and thus have a greatly altered \( k_e \) in renal failure.

From the clinical point of view it is important to be able to predict what will happen to the pharmacokinetics of an antibiotic when renal function is reduced, and help for this can be found by obtaining the relative values of \( k_e \) and \( k_{ar} \) in normal subjects from the literature (Smith & Rawlins, 1973; Dettili, 1976) or from the manufacturers. It is also possible to predict them from knowing the fraction \( f \) of a parenteral or absorbed dose excreted unchanged in the urine of normal subjects provided there is no alteration of \( k_{ar} \) (for example, enhancement or depression of metabolism) (Welling, Craig & Kunin, 1975) since:

\[
 f = \frac{k_{ar}}{k_e + k_{ar}}.
\]

For antibiotics with a high value for \( k_e \) compared to \( k_{ar} \), it follows that in renal failure \( k_e \) will decrease markedly, which will lead to a significant increase in the plasma half-life, \( T_{1/2} \), since:

\[
 T_{1/2} = \frac{0.693}{k_e}.
\]

Thus the principal pharmacokinetic consequence of reduced elimination of an antibiotic by the kidneys may be an increase in the plasma half-life, and a number of clinically important consequences stem from this.

Unabated dosing will lead to higher plasma concentrations since, provided the volume of distribution of the antibiotic remains unaltered, the plasma concentrations at steady state depend only on the rate of input of antibiotic to the body and the rate of clearance (\( CL \)). Thus a dosage regimen for normal renal function that is unmodified or insufficiently modified in the presence of reduced renal function will inevitably lead to higher plasma concentrations. This can be expressed by:

\[
 Cp_m = \frac{(F)(Dose)}{Cl \times \tau},
\]

where \( Cp_m \) = average steady state concentration in the plasma; \( F \) = fraction of the dose absorbed (unity for iv administration), \( Cl \) = plasma clearance, and \( \tau \) = dosing interval.

When such a formula is used it is essential to ensure that there is agreement in the expression of the units: for example, clearance in l/h, concentration in mg/l, dosing interval in, dose in mg, etc. Clearance is related to the plasma half-life:

\[
 T_{1/2} = \frac{0.693 \times V_d}{Cl},
\]

where \( V_d \) = volume of distribution.

A reduced maintenance dose will be needed to give the same plasma concentrations as those occurring during normal renal function. Many of the toxic effects of antibiotics are not related to concentrations so the increased
plasma concentrations resulting from a prolonged half-life may not give rise to concern, at least if they are moderate. Indeed, they may result in improved efficacy, their only penalty being perhaps a lost opportunity to reduce dosage and thus cost. With some antibiotics, however, there is a closer relationship between toxicity and concentration so that it is essential to control the latter by reducing dosage in renal failure. This can be achieved by using smaller individual doses, prolonging the dosing interval, or both; there is no clear evidence which is generally the most satisfactory in the treatment of infection by antibiotics. There may well be no necessity to reduce the initial dose (see below). With oral agents it may not be possible or desirable to break into the dosage form, such as tablets or capsules, and even with injectable agents fractional doses may be difficult to measure accurately, so prolonging the dosing interval may be the only practical option. The maintenance dose to produce the desired average steady state concentration is given by:

\[
\text{Maintenance dose} = \frac{C_l \times C_p \times \tau}{F}
\]

The time to reach steady state will be prolonged and a loading dose may be indicated. Independent of the ultimate (steady state) plasma concentrations, route of administration, or dosing interval is the time to reach those concentrations, which will always be about five times the plasma half-life (Van Rossum, 1968). Theoretically, it takes \( 1 \times T_{1/2} \) to reach 50%, \( 2 \times T_{1/2} \) to reach 75%, \( 3 \times T_{1/2} \) to reach 87.5%, and \( 4 \times T_{1/2} \) to reach 93.75% of the steady state concentration. Thus in renal failure the time to reach the desired plasma concentrations may become unacceptably prolonged and it may be necessary to use a loading dose, even when prescribing an antibiotic with which one would not be indicated in the presence of normal renal function. Loading doses are not often used with antibiotics since the latter are frequently given with dosing intervals, typically 6 or 8 h, considerably longer than the plasma half-life; a half-life of 0.5-2 h is common amongst the β-lactams and aminoglycosides. Accumulation in the plasma therefore does not occur on repeated dosing when renal function is normal.

Where it is important to achieve optimal plasma levels quickly, as when a serious infection is being treated, and the plasma half-life is prolonged because of impaired renal function or other causes, it may be important to give a loading dose even though the maintenance dosage has been appropriately reduced. Perhaps the best example of this is with aminoglycosides, the plasma concentrations of which must fall into a narrow range and whose plasma half-life may be considerably prolonged. There is controversy about the size of the loading dose in renal failure (Fabre & Balant, 1976), but a useful approximation is given by:

\[
\text{Loading dose} = \frac{V_d \times C_p}{F}
\]

It should be noted that it is unaffected by half-life.

The fluctuation in concentration between doses will be smaller. When the dosing interval is much longer than the half-life virtually all the antibiotic is eliminated by the next dose and each dose can therefore be looked upon as a loading dose. Clearly this will give a wide variation in the plasma concentrations about each dose, but this may be acceptable for many antibiotics because of their high therapeutic index. When the converse exists, that is the dosing interval is much shorter than the half-life very little fluctuation in concentration occurs between doses. Thus, if half-life increases and the same dosing interval is maintained, the variation in concentration between intermittent doses is smaller.

A corollary to this is that the timing of samples for plasma assay becomes less critical. When half-life is short only a small variation in the dose-to-sample time may have a profound effect on the observed concentration, which is confusing if it is being followed on, say, a daily basis. When the half-life is very long the effect on the interpretation of an assay result is small in relation to its timing. The time for drug elimination from the body after therapy ceases will be increased. This generally has no great clinical consequence with antibiotics, but may be important for the timing of follow-up cultures, in the assay of plasma or urine samples for antibiotic if there is potential technical interference from one previously administered, or when a drug interaction might occur. In quantitative terms, final elimination is the converse of accumulation, for example, it takes \( 3 \times T_{1/2} \) to eliminate 87.5%.

The effect of renal function on plasma half-life holds whether the renal impairment is acute or chronic and is not dependent on the general health of the patient, but other pharmacokinetic effects may be. For example, in acute renal failure, hepatic function may be
affected and thus antibiotic metabolism.

**Distribution volume may be altered.** As a consequence of renal failure a number of factors may alter the volume into which an antibiotic is distributed. These include the presence of oedema or dehydration, altered penetration into erythrocytes, and reduced plasma protein binding. The last may occur as a result of hypoalbuminaemia or because of lowered binding to albumin, as occurs with acidic antibiotics in renal failure (Craig *et al.*, 1976). Lower plasma protein binding is probably only clinically important with antibiotics having high binding (> 90%) in normal conditions and the ultimate effect of this decrease is complex since potentially a greater amount of free drug is available for elimination and distribution. The concentration of free drug in the plasma will therefore tend to be the same as in the unperturbed state, but the total concentration (the one usually measured by assays) will be lower.

**Absorption may be altered.** Reduced gastrointestinal absorption in terms of both rate and extent has been described for antibiotics in renal failure. Although studies have not been reported, it is easily possible to envisage that intramuscular absorption may be reduced in very ill patients, and intravenous administration would be the route of choice.

**The concentration of active antibiotic in the urine may be lower.** When renal clearance is lowered, the concentration of antibiotic in the urine diminishes relative to the plasma concentrations. Urinary concentrations may be maintained by increased plasma concentrations but the latter are not always desirable. With antibiotics with a relatively high renal compared to non-renal elimination adequate urine concentrations are often maintained down to low levels of renal function, but if non-renal elimination normally plays a substantial part in the excretion of an antibiotic urinary concentrations may soon become inadequate as renal function diminishes. Such agents are best avoided, if possible, for treating urinary infection in renal impairment. With others it may be possible to increase the dosage and thus obtain adequate urinary concentrations.

**Metabolism may be affected.** In patients severely ill with acute renal failure hepatic metabolism may be impaired but in the relatively fit patient, such as one on chronic haemodialysis, it may be either enhanced as a compensatory mechanism or decreased. Thus the relative importance of the fraction of drug eliminated by non-renal mechanisms is hard to predict without knowledge of both individual drugs and patients.

**Antibiotic metabolites may accumulate.** Active drug metabolism generally converts parent substances to more polar entities to facilitate their excretion by the kidneys and liver. This biotransformation rarely enhances the microbiological activity of an antibiotic and often reduces or removes it. Biotransformation may do little to modify antibiotic toxicity and may even increase it. Some antibiotics, such as the β-lactams, undergo non-metabolic chemical degradation because of chemical instability to give inactive derivatives, such as the analogous penicilloates from penicillins. It is important to realise that many antibiotic metabolites are excreted primarily by the kidneys and may themselves accumulate in renal failure, perhaps enhancing antimicrobial action if they are microbiologically active, increasing toxicity, and interfering in assay procedures. There is, in general, little published information on the pharmacokinetics of metabolites and their toxicity since until recently analytical techniques, such as HPLC, have not been available in clinical laboratories. Metabolites are, furthermore, not welcome news as far as the pharmaceutical industry is concerned since they represent a possible hazard to registration and no benefit, and research into metabolites is therefore sometimes not encouraged. There is a need for the systematic study of metabolites and their relationship to toxicity in particular. For example, while it is known that the acetylated derivatives of sulphonamides are toxic and accumulate in renal failure, it is not known if the neurotoxicity of benzylpenicillin in renal failure is due to accumulation of the antibiotic itself or its derivative which may well also undergo accumulation. One pharmacokinetic fact is indisputable, that the apparent half-life of a metabolite is always equal to or exceeds that of the parent antibiotic whatever its true half life. This is because the half-life of the metabolite is related to a series of rate constants, such as those of its elimination of parent drug, the rate of biotransformation, and the rate of its own elimination, any one of which can be the rate limiting step. Thus metabolites tend to accumulate in renal failure if dosage is adjusted given normal plasma levels of the parent drug. Examples are desacetyl cephalothin (Nilsson-Ehle & Nilsson-Ehle, 1979) and desacetyl cefotaxime (Wise, Wright & Wills, 1981). Since it is not usually possible
to administer a metabolite in the absence of its parent drug to human subjects because of a lack of dosage forms, determining its real pharmacokinetics, as opposed to those apparent when it is derived from its parent drug, presents a difficult problem. When the pharmacokinetics are derived from experiments it is possible that the true half-life of a metabolite might turn out to be much shorter than the apparent half-life, as for desacetyl cefotaxime in normal volunteers (Ings et al., 1985). The recent interest in quinolone antibiotics has stimulated research into metabolites, but more information is needed on older agents, particularly those used regularly in patients with poor renal function.

D. S. REEVES
Department of Medical Microbiology, Southmead Hospital, Bristol, UK

References


These two leading articles were based on contributions to a meeting of the British Society for Antimicrobial Chemotherapy: 'Pharmacokinetics in Altered States', held in Edinburgh on 8 May 1987—EDITOR.