Prescribing in liver disease

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Abstract

Patients with liver disease often require drug therapy. Since the liver is the main site of drug detoxification and elimination in the body, each patient's need for therapy must be carefully assessed; the choice of drug, its dose, and duration of therapy must be carefully considered in order to avoid adverse effects. Ideally, one should choose a drug that has a high therapeutic index, is largely devoid of pharmacokinetic and pharmacodynamic interactions and hepatotoxic effects, and is renally eliminated. However, the ideal drug with these properties is often not available, and in such cases the dose and drug should be individualized to the patient, who should then be carefully monitored, the duration of treatment being kept as short as possible. The British National Formulary contains useful information on drugs that should be avoided or their dosage modified in patients with liver disease.

Keywords Hepatotoxic drugs; liver disease; pharmacodynamics; pharmacokinetics; prescribing

What's new?

There is increasing evidence that liver disease can have major effects on the pharmacodynamics of drugs. The complex effects of liver disease therefore provide a better mechanistic explanation for why the risk of drug–drug interactions, and adverse drug reactions, is increased in these patients, further highlighting the need to use the lowest drug dose for the shortest duration possible.

Patients with liver disease often require drug treatment, either for their liver disease and its complications, or for other concomitant conditions. However, liver disease has major effects on drug response, which exposes these patients to a higher risk of drug–drug interactions (DDIs). In one survey 13% of all DDIs led to an adverse drug reaction, which were the most in patients with the most severe hepatic impairment.[1] Prescribers should be aware of the way in which drug response can be affected in patients with liver disease, in order to ensure safe and effective therapy. Drug regulatory agencies such as the US Food and Drug Administration (FDA) require pharmacokinetic studies to be undertaken in patients with hepatic impairment when hepatic metabolism accounts for 20% or more of the elimination of a drug under development, and/or if the drug has a low therapeutic index.[2]

The liver and drug metabolism

The liver is the main site of drug metabolism. This is primarily a detoxification mechanism whereby the body converts pharmacologically active lipid-soluble drugs into inactive hydrophilic metabolites, which can then be excreted by the kidneys.[3] On occasions, metabolic enzymes are also needed for conversion of pro-drugs to their active components. Whereas metabolism in the liver is important for lipid-soluble drugs, renal excretion is more important for hydrophilic drugs (Figure 1). As a general rule, therefore, drugs that undergo hepatic metabolism are more likely to require dosage alteration[4,5] (of either the loading or maintenance dose or both, especially if their therapeutic index is low) in patients with liver impairment than those drugs that predominantly undergo renal excretion, although there are exceptions (see below).

Drug disposition can be thought of as occurring in three phases (Figure 1):

- Phase I pathways are metabolic reactions catalysed by a superfamily of cytochrome P450 (CYP) enzymes located in the endoplasmic reticulum. Each CYP isoenzyme varies in terms of expression and substrate specificity (Table 1).
- Phase II reactions are performed by various enzymes including the glucuronyl transferases, N-acetyl transferases and glutathione-S-transferases, which are located in both the endoplasmic reticulum and the cytosol.
- The phase III pathway is represented by active drug transport processes across cellular membranes rather than enzyme-catalysed reactions; these include both efflux (e.g. P-glycoprotein) and influx (e.g. organic anion transporters) transporters.

Effect of liver disease on pharmacokinetics:[3,5,6] the effect of liver disease on drug metabolism depends on various factors, including:

- The severity of the liver disease – because of the enormous reserve of the liver parenchyma, impaired hepatic elimination of drugs occurs only in severe disease.
- The enzyme responsible for drug metabolism – in general, phase II metabolic enzymes are affected to a lesser extent than phase I enzymes; the effect on the different P450 isoforms also varies (Table 1). CYP3A4 metabolizes more than 50% of drugs and its reduction in cirrhotic livers is likely to cause the biggest problem.
- The type of liver disease – a cholestatic pattern is more likely to affect drug transporter proteins (phase III pathways), whereas phase I metabolism is relatively spared; by contrast, acute hepatic inflammation is more likely to down-regulate CYP enzyme expression via a nitric oxide-dependent pathway.

A decrease in hepatic clearance may result in increased drug concentrations in serum and potential toxicity (Figure 2), particularly for drugs with a low therapeutic index. For pro-drugs, reduced conversion to the active compound results in a reduced therapeutic effect.

Other effects: liver disease can also affect drug pharmacokinetics through other mechanisms:[4,6]

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Competing interests: none declared.

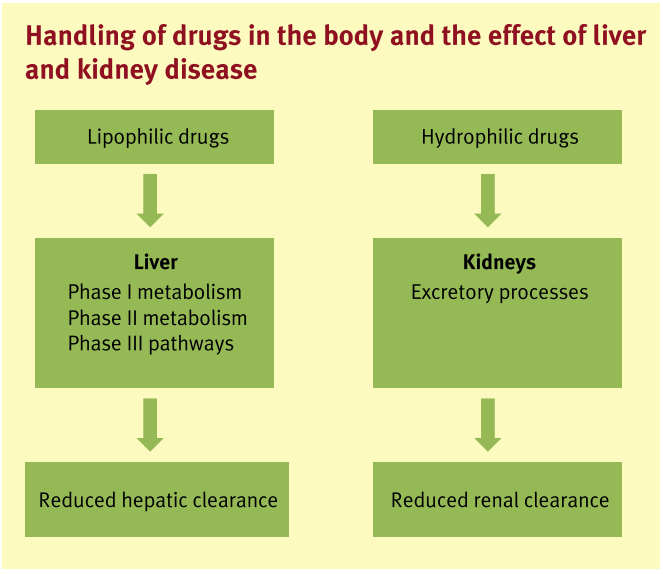

Figure 1

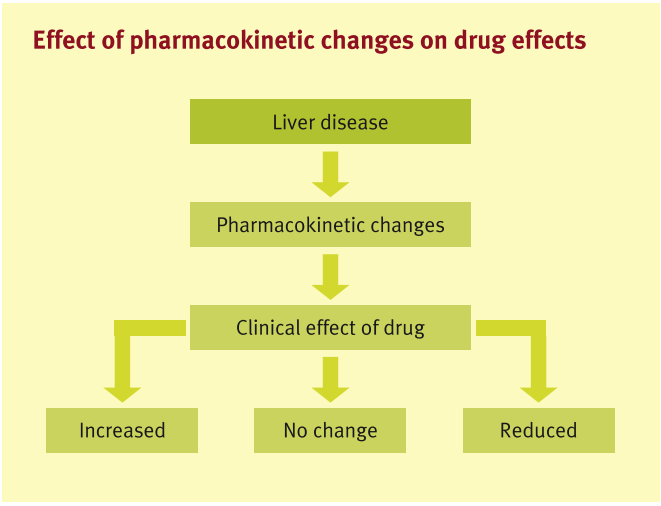

Figure 2

Changes in drug absorption — gut motility is altered in patients with cirrhosis, probably as a result of abnormal concentrations of gut hormones such as motilin. The net result is a delay in gastric emptying and orocaecal transit, causing a reduction in the rate but not the extent of absorption.

Changes in drug distribution — chronic liver disease is characterized by hypoproteinaemia. This may result in a higher fraction of free drug, particularly when the degree of protein binding in the healthy state is >90%. The clinical importance of this may be manifest only in patients with severe liver impairment because of the high metabolic reserve of the liver. The volume of distribution of hydrophilic drugs, such as digoxin, will be increased in patients with oedema and/or ascites; this may require the use of higher loading doses (based on the patient's weight), but maintenance dosage may not need to be changed unless renal function is also affected.

Effect of ascites — Ascites can affect the volume of distribution, bioavailability and elimination half-life of some drugs. For example, doxorubicin accumulates in ascitic fluid. The volume of distribution and half-life of furosemide, which is used for treatment of ascites, are increased to twice normal values in patients with ascites, and the drug's natriuretic potency is reduced.

Changes in liver blood flow — blood flow to the liver may be decreased generally or may bypass the liver as a result of portosystemic shunting in patients with cirrhosis. The effect of this depends on the drug and its degree of extraction by the liver; in general, the higher the extraction by the liver, the more important is blood flow (in relation to metabolism) in determining pharmacokinetics. Drugs with a high extraction ratio, such as certain β-adrenoceptor blockers, calcium channel antagonists, antipsychotics, sedatives and antidepressants, will undergo considerably less first-pass metabolism, resulting in a marked increase in bioavailability. Loading and maintenance doses should be decreased to take account of this.

Changes in renal excretion — renal elimination of hydrophilic drugs (or hydrophilic metabolites) is affected in patients with severe and rapidly advancing hepatic disease who develop hepatorenal syndrome. However, we now know that even moderate hepatic impairment (through mechanisms that are unclear) reduces renal clearance, necessitating a reduction in the maintenance dosage of renally eliminated drugs. Serum creatinine is an insensitive marker of glomerular filtration rate in patients with cirrhosis because of their reduced muscle mass and reduced conversion of creatine to creatinine in the liver; creatinine clearance should be measured, but even this can over-estimate glomerular filtration in patients with cirrhosis (see *Medicine* 2015; **43**(9): 545—549).

Cytochrome P450 (CYP) isoforms involved in phase I drug metabolism in humans

P450 isoform	Substrates	Effect of liver disease on P450 activity
• CYP1A2	Clozapine, theophylline	↓↓↓
• CYP2A6	Halothane, methoxyflurane	↓↓
• CYP2C9	Diclofenac, losartan, warfarin	↓
• CYP2C19	Citalopram, diazepam, omeprazole	↓↓↓
• CYP2D6	Codeine, haloperidol, metoprolol, nortriptyline	↔
• CYP2E1	Enflurane, halothane, paracetamol	↓
• CYP3A4	Amiodarone, carbamazepine, ciclosporin, tacrolimus, diltiazem	↓↓

Only a few substrates are listed for each P450 isoform.

Table 1