Prescribing in liver disease

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Abstract

Patients with liver disease often require drug therapy. Because the liver is the main site of drug detoxification and elimination, each patient's need for therapy must be carefully assessed; the choice of drug, its dose and the duration of therapy must be carefully considered 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, so the dose and drug should be individualized to the patient, who should then be carefully monitored, with the duration of treatment 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; MRCP; pharmacodynamics; pharmacokinetics; prescribing

Key points

- Liver disease affects drug pharmacokinetics, which can increase the risk of drug–drug interactions and adverse drug reactions
- Doses of lipophilic drugs, particularly those with a low therapeutic index, should be reduced when there is a ≥2-fold increase in the area under the curve in hepatic impairment
- First-pass metabolism of drugs with high hepatic extraction is reduced in liver disease, necessitating a reduction in the loading and maintenance doses of oral formulations
- Liver disease also affects drug pharmacodynamics, which can either reduce or increase the effect of a drug, and can lead to serious adverse drug reactions
- Start with low doses, increasing the dosage with careful monitoring; avoid concomitant use of drugs that interact — the effects are more severe in these patients
- The effects of drug-induced hepatotoxicity are more severe in patients with liver disease because of reduced hepatic reserve

Introduction

Patients with liver disease often require drug treatment, either for their liver disease and its complications, or for other common concomitant conditions such as cardiovascular disease. 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; most adverse drug reactions occurred in patients with the most severe hepatic impairment.[1]

To ensure safe and effective therapy, prescribers should be aware of the way in which drug responses can be affected in patients with liver disease. Drug regulatory agencies such as the US Food and Drug Administration 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] Furthermore, dose reduction is required when there is a ≥2-fold increase in the area under the curve in hepatic impairment.

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 the loading or maintenance dose or both, especially if the therapeutic index is low) in patients with liver impairment than are 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 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] the effect of liver disease on drug metabolism depends on various factors:

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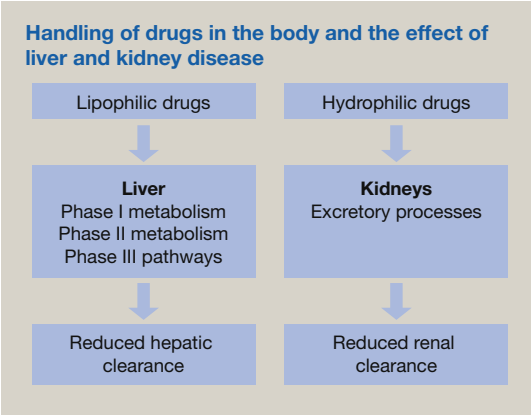

Figure 1

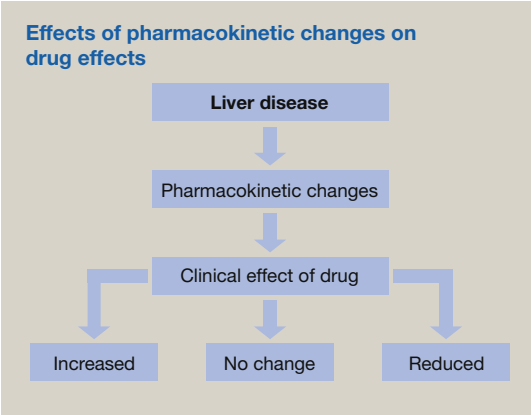

Figure 2

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

- 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 >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 downregulate CYP enzyme expression via a nitric oxide-dependent pathway.

A decrease in hepatic clearance can result in increased drug concentrations in serum and potential toxicity (Figure 2), particularly for drugs with a low therapeutic index. For prodrugs, 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]

Changes in drug absorption – mucosal inflammation, oedema and changes in gut motility in patients with cirrhosis can affect drug absorption. Gastric emptying and orocaecal transit are reduced because of changes in the gut hormone motilin.

Changes in drug distribution – chronic liver disease is characterized by hypoproteinaemia. This can 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, is increased in patients with oedema and/or ascites; this can necessitate 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 and oedema – 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 to treat 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 can be decreased generally or can bypass the liver as a result of portosystemic shunting in patients with cirrhosis. The result depends on the drug and its degree of extraction by the liver and presystemic metabolism in the gut; 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, 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 overestimate glomerular filtration in patients with cirrhosis (see *Medicine* 2019; **47**(10): 679–683).

Effect of liver disease on drug pharmacodynamics: drug response in liver disease is also determined by pharmacodynamic changes.[3,4] These can result in increased or decreased sensitivity, or an increased risk of toxicity (Figure 3), through changes in the function of other organs such as the brain and kidneys. The effects of drugs acting on the central nervous system, such as opioid analgesics, anxiolytics and sedatives, are increased, possibly because of increased sensitivity and/or activity of the γ-aminobutyric acid system. Indeed, hepatic encephalopathy can be precipitated by such drugs.

By contrast, the effect of β-adrenoceptor blockers is reduced in patients with cirrhosis, which may be related to a reduction in β-adrenoceptor density. Similarly, the effect of diuretics is less because of a change in nephron number and function. It is also known that transjugular intrahepatic portosystemic shunts can increase baseline QTc prolongation; caution should therefore be exercised in such patients when considering the use of drugs known to increase QT interval. Therapy with H_2-blockers and proton pump inhibitors can increase the risk of spontaneous bacterial peritonitis and other infections, including *Clostridium difficile* colitis.[4]

Use of potentially hepatotoxic drugs

There is no evidence that patients with liver disease are at increased risk of further liver damage when exposed to drugs known to cause idiosyncratic hepatotoxicity. However, in view of the reduced hepatic reserve, any liver damage induced by the drug can have more severe clinical consequences. With dose-dependent hepatotoxins, use of high doses on one occasion (e.g. paracetamol overdose) or cumulatively (e.g. methotrexate) increases the risk of liver toxicity in patients with pre-existing liver impairment. Nevertheless, the potential risk of hepatotoxicity should not deter prescribers from using drugs (such as statins) whose benefits far outweigh the risk of liver injury.

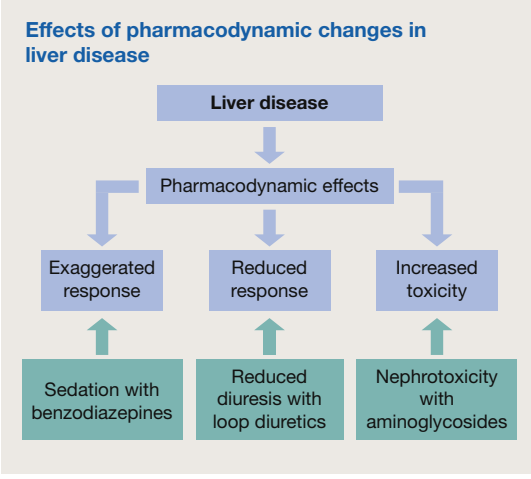

Figure 3

General rules for prescribing in liver disease

Patients must be assessed carefully before prescription of any drug, to determine the risks and benefits. Several factors must be considered:

- How serious is the condition that needs to be treated, and what are the likely consequences of withholding treatment?
- How impaired is the liver function? As there are no good tests to assess liver function, the Child–Pugh score can be used at the bedside to gauge the severity of liver dysfunction.
- What drug treatments are available?
- Are the efficacies of the different treatments equivalent?
- What are the adverse effects of the different treatments?
- Are there any drugs the patient is currently taking that can be stopped safely, thereby reducing the probability of a DDI?

When several drugs are available to treat the same condition, the drug with the highest therapeutic index should be chosen. However, given the major changes in pharmacokinetic and pharmacodynamic parameters in patients with liver disease, the therapeutic index may not be equivalent to that in patients without liver disease. Therefore, it is also important to consider other factors.

- **Is the drug metabolized by the liver?** Hepatic impairment reduces the clearance of such drugs. For drugs with a low therapeutic index (e.g. phenytoin, theophylline), this leads to a disproportionate increase in drug concentration and hence toxicity; a reduction in dosage is therefore necessary. However, unlike in renal failure, there is no easy means to calculate the required dosage change in individuals with hepatic impairment; an estimate must suffice, followed by careful observation of therapeutic response and adverse effects, and therapeutic drug monitoring when available, with further dosage adjustment as necessary. Table 2 lists some of the drugs requiring dosage reduction in liver disease, and a more complete list is available in the British National Formulary.
- **Does the drug have a high hepatic extraction ratio?** Liver blood flow is a major pharmacokinetic determinant for such drugs, and reduces first-pass metabolism. A reduction in dosage of the oral, but not the parenteral, formulation is required.
- **Will the drug worsen the pharmacodynamic changes seen in liver disease?** Specific examples and mechanisms are shown in Table 2. Non-steroidal anti-inflammatory drugs (NSAIDs) enhance sodium and water retention and worsen ascites; in addition, their effects on platelets, combined with clotting defects, increase the risk of bleeding. Bleeding into the gastrointestinal tract can also cause encephalopathy. Because of the changes in renal function in liver disease, NSAIDs affect intrarenal vasodilatory prostaglandins, and cause renal failure in some patients.

Drugs that should be avoided or their dosage reduced in hepatic disease

Decreased hepatic clearance because of a high extraction ratio
- Phenytoin
- Theophylline
- Antipsychotics

Inhibit clotting factor synthesis
- Warfarin
- Phenindione

Lead to excess sodium and water retention
- Corticosteroids
- Non-steroidal anti-inflammatory drugs (NSAIDs)

Lead to potassium loss
- Corticosteroids
- Diuretics

Can cause hepatic encephalopathy
- Hypnotics/sedatives
- Lithium
- Loop diuretics
- Opioids
- NSAIDs

Increase risk of spontaneous bacterial peritonitis
- Proton pump inhibitors
- H_2-receptor antagonists

Enhance risk of adverse drug reactions
- Angiotensin-converting enzyme inhibitors (hypotension)
- Aminoglycosides (nephrotoxicity)
- Cimetidine (confusion)
- NSAIDs (renal injury and gastrointestinal bleeding)
- Oral hypoglycaemic agents (hypoglycaemia)
- Quinolone antibiotics (central nervous system toxicity)

Table 2

- **Is the drug potentially hepatotoxic?** Drug-induced liver damage has more severe clinical consequences in patients with hepatic impairment. If possible, a non-hepatotoxic drug should be used in preference.

In keeping with good clinical practice, all patients taking drugs should be monitored carefully;[4] the frequency and form of monitoring depends on the drug, the condition being treated and the severity of the liver disease. It is important to prescribe simple regimens and to avoid drugs that interact (as the consequences of interaction can be more severe in these patients[1]). Patients should be informed why the drug is being used and given instructions on whom to contact if they develop adverse effects or their condition deteriorates. It is also important to review patients regularly, and not be afraid of stopping drug therapy. Drugs should always be considered in the differential diagnosis when assessing patients who develop new symptoms and signs. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 69-year-old woman presented with pain in the lower back. The pain was localized and there was no radiation down the leg. It had started after a bout of coughing. The patient has used occasional doses of paracetamol but this did not provide much relief. She had been found to have primary biliary cholangitis, cirrhosis and mild portal hypertension. She was taking ursodeoxycholic acid and propranolol. On clinical examination, there was mild tenderness over L5, but straight leg raising was normal and there were no neurological signs. There were liver stigmata, mild ascites, an enlarged liver and mild peripheral oedema, but no evidence of encephalopathy.

Investigation
- X ray of the spine showed no evidence of a vertebral fracture

What is the most appropriate analgesic regimen to control her pain?

A. Give oxycodone
B. Give regular paracetamol
C. Give naproxen
D. Avoid any analgesics and reassure the patient
E. Suggest she try herbal medicines

Question 2

A 56-year-old man presented with a 3-day history of increasing generalized abdominal pain and confusion. He has a past history of alcoholic liver disease, cirrhosis and portosystemic shunting. He also has a history of hypertension, ischaemic heart disease, gastro-oesophageal reflux and irritable bowel syndrome. He was taking a number of drugs, but given his confusion he could not remember their names.

On clinical examination, there was mild confusion, and his temperature was 37.8°C. The abdomen was distended and generally tender. There was tense ascites.

Investigations

- Haemoglobin 135 g/litre (130–180)
- White cell count 17.3 $\times$ 10^9/litre (4.0–11.0)
- Ascitic fluid analysis showed an increase in neutrophils

Of the drugs that he is likely to be taking, which will increase the risk of the probable diagnosis?

A. Ciprofloxacin
B. Lactulose
C. Lansoprazole
D. Propranolol
E. Thiamine

Question 3

A 60-year-old man presented with a 1-day history of confusion, visual hallucinations and tremors. He had a past history of alcoholic liver disease and cirrhosis. He had continued to drink, but over the previous few days had then stopped drinking because he could not get out to the shops. He was taking regular thiamine, fluoxetine, propranolol and spironolactone.

On clinical examination, there was mild confusion, and the heart rate was 100 beats/minute and regular. There was a fine tremor of the hands, which were sweaty. The liver was enlarged to 4 cm below the costal margin, but there was no ascites.

What treatment should be considered for this new presentation?

A. Alcohol
B. Diazepam
C. Increased dose of fluoxetine
D. Increased dose of propranolol
E. Oxazepam