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

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. 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.

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. 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 (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: 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 isoenzymes 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:

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.
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 oro-caecal 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, is 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 hepato-renal 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).

<table>
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<th>Cytochrome P450 (CYP) isoforms involved in phase I drug metabolism in humans</th>
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<td>CYP2E1</td>
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<td>CYP3A4</td>
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Only a few substrates are listed for each P450 isoform.

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Effect of liver disease on drug pharmacodynamics

Drug response in liver disease is also determined by pharmacodynamic changes. 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 as a result of increased sensitivity and/or activity of the γ-aminobutyric acid (GABA) system. Indeed, hepatic encephalopathy may 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 also reduced due to a change in nephron number and function. It is also known that transjugular intrahepatic portosystemic shunts (TIPS) can increase baseline QTc prolongation, and caution should be exercised in such patients when considering the use of drugs known to increase QT-interval. Therapy with H₂-blockers and proton pump inhibitors can increase the risk of spontaneous bacterial peritonitis and other infections including Clostridium difficile colitis.

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 may have more severe clinical consequences. With dose-dependent hepatotoxins, use of high doses on either 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.

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.

- Is the drug metabolized by the liver? Hepatic impairment reduces the clearance of such drugs. For those with a low therapeutic index (e.g. phenytoin, theophylline), this will lead to a disproportionate increase in drug concentration and hence toxicity, and a reduction in dosage is therefore necessary. However, unlike in renal failure, there is no easy means of calculating the required dosage change in those 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; 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, and their effects on platelets, combined with clotting defects, increase the risk of bleeding. Bleeding into the gastrointestinal tract may also precipitate encephalopathy. Because of the changes in renal function in liver disease, NSAIDs affect intrarenal vasodilatory prostaglandins, and in some patients precipitate renal failure.
- Is the drug potentially hepatotoxic? Drug-induced liver damage has more severe clinical consequences in patients with hepatic impairment. If a non-hepatotoxic drug is available, this should be used in preference.
In keeping with good clinical practice, all patients taking drugs should be monitored carefully; 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 (the consequences of interaction may be more severe in these patients). 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 the patient regularly, and not to 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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**Practice points**

- Liver disease affects both pharmacokinetic and pharmacodynamic variables, both of which 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
- First-pass metabolism of drugs with high hepatic extraction is reduced, necessitating a reduction in the loading and maintenance doses of oral formulations
- Start at low doses, increasing the dosage with careful monitoring; avoid concomitant use of drugs that interact — the effects are more severe in these patients
- Choose a hydrophilic drug over a lipophilic compound when available
- The effects of drug-induced hepatotoxicity are more severe in patients with liver disease because of reduced hepatic reserve
Alcohol and the liver

Ewan Forrest

Abstract
Hospital admission with alcoholic liver disease (ALD) has become increasingly common. Although there is a clear relationship between the risk of ALD and the dose of alcohol consumed, additional risk factors include genetic predisposition, gender, nutritional status, obesity, and co-existing liver diseases such as hepatitis C. ALD ranges from steatosis to alcoholic steatohepatitis and established cirrhosis. Several mechanisms are involved in the pathophysiology of ALD, including oxidative damage secondary to alcohol metabolism, and endotoxaemia leading to tumour necrosis factor α-mediated cell damage and death. Diagnosis requires a combination of a history of alcohol excess, clinical evidence of liver disease and compatible laboratory investigations, and the exclusion of other liver diseases. Liver biopsy may be necessary in cases of uncertainty. Presentation varies from incidental blood test abnormalities through to overt liver failure. The key to management is long-term abstinence and care should be delivered in conjunction with addiction services. Protein—calorie malnutrition is common and should be addressed along with specific thiamine replacement. Acute severe alcoholic hepatitis has a high mortality, and prognostic scores, such as the discriminant function and the Glasgow alcoholic hepatitis score, have been derived to identify those at highest risk and those who may derive short-term benefit from treatment with corticosteroids. Cirrhotic patients require hepatoma screening and variceal screening endoscopy. Liver transplant should be considered if the clinical condition does not improve despite a period of abstinence.

Keywords Alcohol; alcoholic hepatitis; alcoholic liver disease; cirrhosis

Epidemiology
In the UK, liver disease is the fifth most common cause of death and this death rate is increasing in contrast to that in many other Western European countries. The major cause of these deaths is alcoholic liver disease (ALD). The average age of death from liver disease is just 59 years, compared with 62–85 years for those dying from cerebrovascular, heart or lung disease. There has been a fivefold increase in cirrhosis among people aged 35–55 years in the last 10 years.2

The population mortality from alcoholic liver disease is proportional to per capita alcohol consumption, and this has been shown to correlate closely with alcohol affordability. The current estimated cost of a hospital admission for a single episode of decompensated ALD is approximately £3400.2 In 2012 in England, one in every eight hospital admissions for ALD resulted in death.3

Risk factors
In addition to the clear relationship to the amount of alcohol consumed, other factors influence the development of ALD. Women are more susceptible to the hepatotoxic effects of alcohol and develop ALD more quickly than men who consume an equivalent daily amount of alcohol.4 The most significant diet-related risk factor is obesity, with several studies showing that obesity is the single most important risk factor determining the risk of cirrhosis in heavy drinkers.5 Twin studies have indicated the importance of genetic susceptibility to ALD, showing that monozygotic twins have a higher prevalence of alcohol-related cirrhosis than dizygotic twins.6 Such studies suggest that genetic factors may represent up to 50% of an individual’s susceptibility to ALD, although the search for specific polymorphisms has so far been unsuccessful.7 Co-existent hepatitis C infection increases the risk of cirrhosis 30-fold in those who take alcohol to excess.5

Pathophysiology
The pathophysiology of ALD is complex with multiple mechanisms of possible hepatocyte damage. Metabolism of alcohol to acetaldehyde and then to acetate by their respective dehydrogenases leads to the production of reduced nicotinamide adenine dinucleotide (NADH), which inhibits fatty acid oxidation and promotes fat accumulation. Alternative metabolism of alcohol by the cytochrome P450 enzyme 2E1 leads to the production of reactive oxygen species, causing lipid peroxidation and inflammation.

Alcohol also increases intestinal permeability, leading to endotoxaemia. This causes Kupffer cells in the liver to release tumour necrosis factor α (TNFα), which in turn leads to more oxidative stress. In addition, acetaldehyde may form protein adducts that can act as neo-antigens, triggering immune-mediated damage (Figures 1 and 2). The results of these multiple ‘hits’ on the liver leads to hepatocyte necrosis, but perhaps more significantly apoptosis.

Pathology
The term ALD encompasses alcoholic steatosis, with or without significant fibrosis (in up to 100% of drinkers with a daily alcohol intake of greater than 60 g/day), alcoholic steatohepatitis (in 10–35%), and established cirrhosis (in approximately 15%).9 The natural history of ALD appears to progress liver through steatosis to fibrosis and cirrhosis with some, but probably not all, patients also passing through a phase of alcoholic hepatitis. The steatosis is macrovesicular and predominantly in perivenular hepatocytes. The features of alcoholic hepatitis are a perivenular steatohepatitis, often with Mallory bodies, hepatocyte ballooning, megamitochondria, canicular cholestasis and a neutrophil infiltrate. With repeated episodes of injury, regenerative nodules and perivenular fibrosis develop leading to micronodular cirrhosis.

Diagnosis
The history should document the type and pattern and amount of alcohol consumed. Screening tools for harmful alcohol use include the AUDIT questionnaire or its abbreviated forms, the
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Acute alcoholic hepatitis

Severe acute alcoholic hepatitis has a 28-day mortality of up to 60%. A clinical diagnosis of alcoholic hepatitis still encompasses a wide spectrum of disease. Assessment of the severity of alcoholic hepatitis is vital not only to identify those patients with a poor prognosis, but also to target treatment effectively. The discriminant function (DF) has been used for this purpose; a value more than 32 is associated with a poor prognosis. However, the DF suffers from a lack of specificity and overall accuracy, and relies upon the measurement of prothrombin time, which can vary significantly between different laboratories. The Glasgow alcoholic hepatitis score (GAHS) is a more accurate score that has been validated throughout the UK. A value of 9 or more is associated with a poor prognosis. Both the DF and the GAHS have been used to identify patients who will benefit from specific treatment. The model for end-stage liver disease (MELD) score has been used to assess prognosis in alcoholic hepatitis, but the threshold for identifying poor outcome remains unclear and the MELD score has yet to be shown to identify patients likely to benefit from additional treatment (Table 1).

Use of corticosteroids in alcoholic hepatitis has been controversial. The STOPAH trial, the largest study of alcoholic hepatitis ever performed, has addressed this question. Over 1000 patients with a GAHS less than 9 did not appear to benefit from corticosteroid treatment, whereas those with a GAHS of 9 or more showed improved 28 and 84-day survival. Further analysis of the STOPAH data with regard to the performance of alternative prognostic scores is awaited and may shed light on this area.

A fall in serum bilirubin after a week of corticosteroid treatment is associated with a survival benefit. From this observation the Lille score has been developed to identify complete, partial and non-responders to corticosteroid treatment. However, a simpler index of response — a 25% reduction in serum bilirubin from baseline after approximately 1 week of treatment — may be equally able to identify such ‘responders’ to treatment.

The clinical presentation of alcoholic hepatitis can mimic sepsis. Patients should be screened for infection with a chest X-ray and culture of urine, blood and ascitic fluid as appropriate.

Cirrhosis

The complications of alcohol-related cirrhosis, such as ascites, variceal haemorrhage and encephalopathy, should be managed in the same way as for other forms of chronic liver disease. Patients with cirrhosis should have 6-monthly USS and aP for hepatocellular carcinoma screening, and screening endoscopy for oesophageal varices. Long-term prognosis is closely related to the stage of disease, as assessed by standard chronic liver disease scores such as the MELD score or the Child–Pugh score. Clearly, the prognosis is improved by sustained abstinence.

Liver transplantation

Liver transplant should be considered for those patients whose clinical condition remains poor despite sustained abstinence. Although there is no requirement for a set period of abstinence before considering liver transplant, many patients will improve clinically for up to 6 months after stopping drinking. This improvement might render referral for transplant unnecessary. Those patients who are assessed for transplant require a rigorous psychiatric evaluation. Liver transplant for alcoholic hepatitis has been suggested for those who do not respond to corticosteroids (‘Lille non-responders’), but concerns remain about the suitability of such intervention and whether the Lille score is specific enough to identify those with little chance of survival.

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