Prescribing in liver disease

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Summary

As the liver is responsible for the metabolism of many compounds, knowledge of a patient's hepatic function is required for the safe prescribing of many drugs. Assessing liver function by way of a patient history, examination and blood tests such as serum albumin and bilirubin, as well as prothrombin time, is recommended before prescribing some medications. Liver enzyme concentrations may be useful indicators of hepatocellular damage or enzyme induction. For drugs dependent on hepatic elimination, careful choice of compounds and their dose is prudent if liver function is significantly compromised. Drug interactions must also be considered if a common metabolic pathway exists.

Key words: drug prescribing, hepatic metabolism.

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Introduction

The metabolism of many drugs depends on adequate hepatic function. Drugs with a narrow therapeutic range (that is, with little difference between toxic and therapeutic doses) run the risk of accumulating and causing toxicity in patients with hepatic disease.

The liver receives a dual blood supply with about 20% of blood coming from the hepatic artery and 80% from the portal circulation. The blood flow to the liver is around 20–25% of the total cardiac output. Toxins, infectious agents, medications and serum inflammatory mediators may result in a diverse range of disease processes leading to loss of normal histological architecture, reduced cell mass and loss of blood flow. Consequently, functional liver capacity may be lost.

Assessing hepatic function is necessary so that appropriate adjustment of drug dose can be made. However, this is not always straightforward as there is no single test that reliably measures liver function.

Drug metabolism in the liver

The liver is the principal organ of metabolism in the body although other sites are involved such as the gut wall, kidney, skin and lungs. Drug metabolism, by means of enzyme reactions in the liver, is the body's main method of deactivating drugs. Drug molecules are converted into more polar compounds, which aids their elimination. Generally, metabolism results in the loss of pharmacological activity because transport to the site of action is limited due to reduced lipid solubility, or because the molecule is no longer able to attach to its receptor site. However, in some circumstances drugs are metabolised to more active forms, for example the conversion of codeine to morphine, primidone to phenobarbitone and amitriptyline to nortriptyline.

Concentrations of enzymes involved in both phase I and II reactions vary significantly between individuals with normal hepatic function and even more so between the healthy population and those with hepatic impairment.

Phase I reactions

Most drugs are lipophilic and therefore readily cross the cell membrane of the enterocyte. In the process of liver metabolism these substances are converted into more hydrophilic compounds. Hydrolysis, oxidation and reduction are the three types of phase I reactions that do this in the liver. These mainly involve a subset of mono-oxygenase enzymes called the cytochrome P450 system. The most common reaction is hydrolysis which involves the addition of a molecular oxygen atom to form a hydroxyl group, with the other oxygen atom being converted to water (for example, the conversion of aspirin to salicylic acid). Other types of phase I reactions include oxidation via soluble enzymes such as alcohol dehydrogenase, and reduction (for example nitrazepam).

Phase II reactions

These reactions involve conjugation which is the attachment of molecules naturally present in the body to a suitable link in the drug molecule. Most compounds will have undergone a phase I reaction (for example, addition of a hydroxyl group) before the conjugation step can occur. The main conjugation reaction involves glucuronidation (for example with morphine), but other conjugation mechanisms include acetylation (sulfonamides) or the addition of glycine (nicotinic acid) and sulfate (morphine). Natural substances such as bilirubin and thyroxine may be metabolised by the same pathways. The resulting conjugate molecule is usually pharmacologically inactive and substantially less lipophilic than its precursor so it is more readily excreted in the bile or urine.

In some circumstances the parent compound is a prodrug so the metabolite is active (for example, codeine is converted to morphine). A common cause of capacity limited hepatic metabolism is the amount of the conjugate available. Paracetamol overdose is an example of this situation. With normal prescribed doses of paracetamol, the toxic metabolite (N-acetyl-p-benzoquinone imine or NAPQI) is efficiently detoxified by conjugation with glutathione as a phase II reaction. However, when a large amount of NAPQI is generated, the total quantity of available glutathione may be consumed and the detoxifying process becomes overwhelmed. Phenytoin and warfarin are other drugs where capacity limited hepatic metabolism can occur.

Excretion

Following metabolism, compounds are then either excreted directly into the bile, or re-enter the systemic circulation and are excreted as polar metabolites or conjugates by the kidney.

If excreted in the bile (mainly glucuronidated drugs), the compound enters the biliary duct system and is secreted into the upper small intestine. Then throughout the ileum, these conjugated bile salts (some of which have drugs attached to them) are reabsorbed and transported back to the liver via the portal circulation. This is known as enterohepatic circulation. Each bile salt is reused approximately 20 times and often repeatedly in the same digestive phase. The implications of this process are that compounds may reach high hepatic concentrations resulting in significant hepatotoxicity. Some drugs that undergo enterohepatic cycling to a significant extent include colchicine, phenytoin, leflunomide and tetracycline antibiotics.

Systemic drug availability

After drugs are absorbed from the gut, a proportion of the dose may be eliminated by the liver before reaching the systemic circulation. This pre-systemic or first pass elimination is determined by the hepatic clearance or extraction for the compound. Hepatic clearance depends on three factors:

- extent of drug binding to blood components such as albumin
- blood flow to active metabolic cells, which is dependent on the architecture in the liver
- functional hepatocytes.

The hepatic extraction ratio of a drug will indicate if its elimination is dependent on blood flow and hepatocyte function (highly extracted) or hepatocyte function alone (poorly extracted). Some examples of high and low extraction drugs are listed in Table 1.

Hepatic conditions

Chronic liver disease is more predictably associated with impaired metabolism of drugs than acute liver dysfunction. However, in cases of severe acute liver failure, the capacity to metabolise the drug may be significantly impaired.

In the chronic state, cirrhosis of any aetiology, viral hepatitis and hepatoma can decrease drug metabolism. In moderate to severe liver dysfunction, rates of drug metabolism may be reduced by as much as 50%. The mechanism is thought to be due to spatial separation of blood from the hepatocyte by fibrosis along the hepatic sinusoids.

The use of certain drugs in patients with cirrhosis occasionally increases the risk of hepatic decompensation. An example of this is the increased risk of hepatic encephalopathy in some patients who receive pegylated interferon alfa-2a in combination with ribavirin for the treatment of chronic active hepatitis related to the hepatitis C virus. In addition, co-infection with hepatitis B or C virus, even in the absence of cirrhosis, increases the risk of hepatotoxicity from antiretroviral therapy in patients with coexistent HIV infection.

In the presence of chronic liver disease, there is potential for changing the systemic availability of high extraction drugs, thereby affecting plasma concentrations. A potential consequence of liver disease is the development of portosystemic shunts that may carry a drug absorbed from the gut through the mesenteric veins directly into the systemic circulation. As such, oral treatment with high hepatic clearance drugs such as morphine or propranolol can lead to high plasma concentrations and an increased risk of adverse effects.

Liver damage can also affect drugs with low hepatic clearance. For instance, the effect of warfarin, which has a low extraction ratio, is increased due to the reduced production of vitamin K-dependent clotting factors.

The pharmacokinetic interaction between alcohol and drugs is more complex. An acute ingestion of alcohol may inhibit a drug's metabolism by competing with the drug for the same set of metabolising enzymes. Conversely, hepatic enzyme induction may occur with chronic excessive alcohol ingestion via CYP2E1 resulting in increased clearance of certain drugs (for example phenytoin, benzodiazepines). After these enzymes have been induced, they remain so in the absence of alcohol for several

Table 1

Some examples of drugs with high and low hepatic extraction

High extraction ratio	Low extraction ratio
Antidepressants	Non-steroidal anti-inflammatory drugs
Chlorpromazine/haloperidol	Diazepam
Calcium channel blockers	Carbamazepine
Morphine	Phenytoin
Glyceryl trinitrates	Warfarin
Levodopa	
Propranolol	

weeks after cessation of drinking. In addition, some enzymes induced by chronic alcohol consumption transform some drugs (for example paracetamol) into toxic compounds that can damage the liver.

In the presence of cholestatic jaundice, drugs and their active metabolites that are dependent on biliary excretion for clearance will have impaired elimination. Further impairment will occur if the compound is excreted as a glucuronide and is subject to enterohepatic circulation.

Evaluating hepatic function

A clear patient history with respect to alcohol, illicit drug use and toxic industrial exposure must be recorded. The medication list including supplements such as iron, vitamin A and herbal remedies is vital. A family history of diseases such as alpha-1 antitrypsin deficiency, iron storage diseases, porphyrias and diabetes mellitus may alert the physician to the potential for liver impairment.

It is also important to look for signs of acute or chronic liver disease such as the presence of jaundice, spider naevi, palmar erythema, ascites, abdominal distention, hepatomegaly, splenomegaly and caput medusa. If there is clinical evidence of liver disease, further investigation is required. This includes liver function tests and an ultrasound of the abdomen. A portal vein Doppler study is also recommended to assess for the presence of portal hypertension. A slowing or reversal of portal vein blood flow indicates portal hypertension which may be related to either liver cirrhosis or portal vein thrombosis.

In renal disease, serum creatinine concentration and the glomerular filtration rate provide a reasonable guide to drug dosage requirements. In contrast, there is no single test that measures liver function so a reliable prediction of pharmacokinetics is not possible. Some evaluation of hepatic function is possible by assessing serum albumin and bilirubin, and prothrombin time. However, these parameters are not directly related to drug clearance. Although not directly correlated with liver dysfunction, elevated liver enzymes may raise the suspicion of hepatic impairment requiring further investigation.

The Child-Turcotte score was designed to estimate the operative risk of an alcoholic patient with cirrhosis. The parameters used include serum concentrations of bilirubin and albumin, prothrombin time, nutritional status and ascites. These parameters were modified to substitute degree of encephalopathy for nutritional status and then became known as the Child-Pugh classification (see Table 2).[1] The grades A, B and C may also be a useful indicator of an individual's ability to effectively metabolise a drug. An alternative method for assessing liver dysfunction is the Model for End-Stage Liver Disease (MELD) score (www.unos.org/resources/MeldPeldCalculator.asp).[2] This may be a more accurate method but is less accessible to most clinicians because it involves calculating the score.

Evaluating the drug in question

If a drug is dependent on hepatic elimination, there are several factors to consider when prescribing for patients with liver disease (see box). Determining the hepatic contribution to elimination is paramount and the following general rules should be considered.

Drugs with a narrow therapeutic range that are extensively metabolised by the liver (that is, greater than 20% of their total elimination) should either be avoided altogether (e.g. pethidine) or used with extreme caution (e.g. morphine, theophylline) in patients with significant liver disease.

Drugs with a wide therapeutic range which also undergo extensive hepatic metabolism should be used with caution. In particular, the dosing interval should be increased or the total dose reduced (e.g. carvedilol).

Table 2

Child-Pugh classification [1]

Parameter	Points assigned = 1	Points assigned = 2	Points assigned = 3
Ascites	Absent	Slight	Moderate
Bilirubin, micromol/L	<11	11–45	>45
Albumin, g/L	>35	28–35	<28
Prothrombin time – seconds over control or INR	<4 <1.7	4–6 1.7–2.3	>6 >2.3
Encephalopathy	None	Grade 1–2	Grade 3–4

Total score of 5–6 is grade A or well compensated disease (1 and 2 year survivals are 100% and 85%)

Total score of 7–9 is grade B or disease with significant functional compromise (1 and 2 year survivals are 80% and 60%)

Total score of 10–15 is grade C or decompensated liver disease (1 and 2 year survivals are 45% and 35%)

Depending on hepatic clearance and the therapeutic index of the drug, dose adjustments or drug avoidance may be required in grades B or C chronic liver disease.

Factors to consider when prescribing drugs dependent on hepatic elimination

- Ascertain how much the drug depends on hepatic metabolism for its elimination from the body.
- Determine the degree of hepatic impairment using the Child-Pugh classification (Table 2), hepatic enzyme levels and possibly an ultrasound of the liver with portal vein Doppler study.
- If there is doubt about the degree of hepatic impairment or the drug has a narrow therapeutic index (that is, the upper dose range for efficacy is close to the lower concentration range of toxicity), then lower the recommended starting dose by approximately 50%, and titrate to effect under careful supervision – 'start low and go slow'.
- Determine possible interactions between the new drug and any drugs the patient is already taking.

If hepatic elimination is limited (that is, accounting for less than 20% of total elimination), then the therapeutic range of the compound should be reviewed. If the drug has a wide therapeutic index, then the likelihood of an adverse effect related to hepatic impairment is low. However, if the drug has a narrow therapeutic index, then caution should be exercised as significant hepatic impairment may have a clinically relevant effect on the pharmacokinetics (e.g. lamotrigine).

If greater than 90% of the compound is excreted unchanged in the urine, then hepatic impairment is unlikely to play a significant role in the accumulation of the drug and therefore toxicity.

Conclusion

Prescribing in hepatic impairment is less well defined when compared to guidelines for prescribing in renal failure. Hepatic dysfunction is less overt and may not be apparent until much of the functioning liver is lost. Knowledge of the metabolism of drugs eliminated by the liver is useful along with close monitoring of the patient for unwanted adverse effects related to possible toxicity. When introducing long-term treatment with a drug with high hepatic clearance or a narrow therapeutic index, assess liver function (clinically and with baseline liver function tests). However, once the drug is commenced routine monitoring is costly and its role unclear in most cases of prescribing in patients with hepatic dysfunction.

References

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Further reading

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 55)

1. Liver function tests are unreliable for calculating drug dosing in liver disease.
2. As warfarin has a low extraction ratio, liver damage does not increase its effects.

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