Emily Smith
Paul Desmond

Prescribing in patients with abnormal liver function tests

Background

The prescribing of medicines to patients with abnormal liver function tests (LFTs) requires careful consideration. Every effort must be made to establish the cause of the abnormal liver function. Whether the patient has cirrhosis also needs to be determined, as this will have broad reaching implications for prescribing.

Objective

Two aspects of prescribing medications to patients with abnormal LFTs will be covered in this review: the use of potentially hepatotoxic drugs in patients with abnormal LFTs, and when to consider dose modification in patients with cirrhosis.

Discussion

Idiosyncratic drug reactions are equally common in patients with normal or abnormal liver function. In advanced liver disease, drugs with predominant hepatic metabolism and/or excretion, particularly those with a narrow therapeutic index, should be used with caution. In the presence of decompensated cirrhosis, prescribing practices are likely to need altering.

Keywords

prescribing; liver diseases; pharmaceutical preparations/administration and dosage

CPD

Case study

Deborah, 54 years of age, presents with concerns about the possibility of high cholesterol. She has no significant past history and is taking no prescribed or over-the-counter medications. Her brother, aged 58 years, has displipidaemia and symptomatic coronary heart disease, but there is no other family history of cardiac disease. Deborah is clinically well, with no symptoms of cardiorespiratory disease. She drinks 1–2 glasses of wine 2 days per week, her body mass index (BMI) is 31 with a waist circumference of 96 cm. Clinical examination is otherwise unremarkable. Baseline blood tests are performed, with results shown below (normal ranges are shown in parenthesis):

Full blood	Hb: 135 g/L	(115–165 g/L)
	WCC: 6.8 x 10^9	(4.0–11.0 x 10^9)
	Plt: 340 x 10^9	(150–450 x 10^9)
Renal	Na 140 mmol/L	(135–145 mmol/L)
	K 4.0 mmol/L	(3.7–5.3 mmol/L)
	Ur 4.3 mmol/L	(2.5–8.0 mmol/L)
	Cr 78 µmol/L	(40–85 µmol/L)
Liver	ALT 70 U/L	(<41 U/L)
	AST 90 U/L	(<41 U/L)
	GGT 110 U/L	(<51 U/L)
	ALP 90 U/L	(30–120 U/L)
	Bili 12 µmol/L	(<25 µmol/L)
	Albumin 42 g/L	(35–50 g/L)
International Normalisation Ratio: 0.9 (<1.2)		
Total cholesterol: 7.1 mmol/L (≤5.5 mmol/L)		
Triglycerides: 3.8 mmol (<1.5 mmol/L)		
Thyroid function tests: normal		

On the basis of her abnormal liver function tests (LFTs), viral and autoimmune serology is performed, which is normal. An abdominal ultrasound shows mild hepatomegaly with fatty infiltrate but no evidence of cirrhosis or portal hypertension.

What is the cause of Deborah's abnormal LFTs, and is statin therapy appropriate?

Case discussion

The most likely cause of Deborah's abnormal LFTs is non-alcoholic fatty liver disease (NAFLD). Non-alcoholic fatty liver disease encompasses a spectrum of pathologic conditions, ranging from steatosis to steato-hepatitis (NASH) and cirrhosis. Mildly elevated alanine transaminases (ALT) and gamma-glutamyl transpeptidase (GGT) are commonly seen in this condition. Bilirubin is usually normal unless there is established cirrhosis.

In evaluating the cause of abnormal liver function in any patient, it is important to recognise the common causes of liver disease, including NAFLD, acute and chronic viral infections, biliary disease, alcohol use, drug toxicities (commonly antibiotics, anticonvulsants, paracetamol), herbal medicines and, more rarely, autoimmune diseases, including coeliac disease. *Table 1* lists the antibiotics and anticonvulsants commonly prescribed by general practitioners that may be hepatotoxic. It also lists some non-prescribed preparations that may be hepatotoxic. The cause can usually be determined on the basis of a simple history, examination and viral and autoimmune serology. Abdominal ultrasound can often assist in the diagnosis of extra-hepatic causes of abnormal LFTs, including biliary disease, and can also assess hepatic anatomy and evaluate for radiological evidence of portal hypertension.

On the basis of clinical, haematological and biochemical assessments, and radiological imaging, there is no evidence that this patient has cirrhosis. There is no stigmata of chronic liver disease on examination. Hepatic synthetic function, assessed by measurement of INR and albumin, is preserved. Platelet count, used as a surrogate marker for splenomegaly and portal hypertension, is normal in this patient. Abdominal ultrasound is useful if there are ultrasound features of portal hypertension (splenomegaly, enlarged main portal vein, ascites, recanalisation of the paraumbilical vein or the presence of porto-systemic shunts). In this patient, abdominal ultrasound does not show evidence of portal hypertension.

The most common clinical hepatic manifestation of statin therapy is asymptomatic elevation in aminotransferases (often transient) and this appears to be a class effect.[1] The incidence of this abnormality with different statins in less than 3% and there is a minor dose-related increase in its incidence.[2] There does not appear to be an increased risk of hepatotoxicity from the use of statins in patients with NAFLD.[2]

There is little evidence to suggest that statin-induced liver injury is more likely in patients with abnormal LFTs or cirrhosis. Given the established cardioprotective benefits of statin therapy in patients with dyslipaedemia, we would recommend statin therapy for this patient. The benefits of statin therapy on hepatic histology and liver enzymes in patients with NAFLD have not been demonstrated in large randomised trials and therefore this treatment cannot be recommended for NAFLD alone in the absence of other indications for statin therapy.[3] In this patient, as in all patients when commencing statin therapy, aminotransferase levels should be monitored and the patient should be assessed clinically for signs of liver toxicity or muscle damage.

Clinical pharmacokinetics and drug metabolism in patients with liver disease

Drug metabolism in the liver

The liver is the principal organ of metabolism in the body and plays a central role in the clearance and transformation of chemicals, making drug-induced liver injury an important phenomenon.

Drug-induced liver injury

Medicines may cause acute or chronic liver damage, depending on their mode of action. Hepatotoxic agents, including medicines, fall into two categories:

- intrinsic and obligatory liver toxins (eg. paracetamol, methotrexate) with dose dependent and predictable adverse effects
- idiosyncratic hepatotoxins (eg. statins, amoxicillin, azathioprine) with non-predictable and non-dose dependent liver toxicity.[4]

In the case of idiosyncratic hepatotoxins, there is no increased risk of hepatotoxicity in patients with abnormal LFTs or cirrhosis. However, it must be considered that in the cirrhotic patient, hepatic reserve is limited in the event of drug-induced hepatocellular or cholestatic injury. Therefore, prescribing any drugs with potential hepatotoxicity in the cirrhotic population should be done with caution, as any drug-related hepatic injury may precipitate hepatic decompensation.

Prescribing of medicines with intrinsic and obligatory hepatotoxicity needs careful consideration in the cirrhotic population for reasons that will be discussed. However, in patients with abnormal LFTs in the absence of cirrhosis, drug metabolism is unlikely to be significantly affected.[4]

Table 1. Common medications and supplements that may cause hepatic toxicity[11,12]

Antibiotics	Anticonvulsants	Herbal and dietary supplements
• Amoxicillin/clavulanate • Flucloxacillin • Erythromycin • Sulfamethoxazole/trimethoprim • Tetracyclines • Quinolones • Nitrofurantoin • Isoniazid • Minocycline	• Sodium valproate • Phenytoin • Carbamazepine	• Black cohosh • Chinese herbal medicines (eg. Ba Jiao Lian, Ma Huang, Jin Bu Han) • Germander • Kava kava • Noni juice • Pennyroyal (when taken orally) • Usnic acid

Why is drug metabolism impaired in cirrhosis?

The liver is a primary site of drug metabolism. Several physiological changes occur in cirrhosis that impact on drug availability, increasing the risk of hepatotoxicity. There are multiple steps in the drug biotransformation in the liver. These steps are dependent on two factors: hepatic blood flow and metabolic capacity of the liver. In patients with liver cirrhosis, altered pharmacokinetics occurs as a result of multiple physiological changes including:

- reduced liver cell mass
- shunting of the blood through porta-systemic collaterals (occurring as a result of portal hypertension)
- reduction in the concentration of drug-binding proteins (albumin is reduced in those with impaired hepatic synthetic function)
- altered pharmacodynamics.

The impairment of drug metabolism is proportional to the liver dysfunction.[5] Patients with compensated cirrhosis and near-normal synthetic function will have minimal impairment of drug metabolism compared to patients with decompensated cirrhosis with significant synthetic dysfunction and portal hypertension.[6] There are no evidence based guidelines for the use of medications in patients with cirrhosis, but we recommend that patients be assessed on an individual basis and that decisions made about prescribing be based on factors such as synthetic function, nutritional status, renal function and the presence or absence of portal hypertension.

Evaluating hepatic function: is there cirrhosis?

Liver biopsy remains the gold standard for the diagnosis and assessment of severity of hepatic fibrosis and cirrhosis. Its invasiveness and susceptibility to sampling error however, demand the need for non-invasive diagnostic modalities.[7] Simple evaluation of serological markers of hepatic synthetic function, as well as platelet count, are useful if there is concern about significant hepatic impairment. In cirrhosis there is often evidence of hepatic synthetic dysfunction: albumin is low and the International Normalisation Ratio (INR) is often raised. Several mechanisms reduce platelet count in patients with cirrhosis, including platelet consumption from splenomegaly, reduced hepatic production of thrombopoietin and bone marrow suppression.

No single test measures liver function, making a reliable prediction of pharmacokinetics impossible.[5] As impairment of drug metabolism is proportional to liver dysfunction, estimation of the severity of cirrhosis should be attempted. Patients with compensated disease are likely to have more predictable drug metabolism and are less likely to require drug dose adjustment. Patients with decompensated cirrhosis will have clinical signs including encephalopathy, jaundice or ascities. Patients with thrombocytopaenia or signs of portal hypertension on abdominal ultrasound are more likely to have advanced liver disease and are a risk of decompensation. It is these patients in whom medications with predominant hepatic metabolism should be prescribed with great caution.

Table 2. Medications with extensive hepatic metabolism and/or high hepatic extraction commonly prescribed in general practice[13]

- Antidepressants
- Chlorpromazine/haloperidol
- Calcium channel blockers
- Morphine
- Glyceryl trinitrates
- Levodopa
- Propranolol
- Diazepam
- Warfarin

In patients with advanced liver disease we recommend prescribing hepatically metabolised and excreted medications at a lower dose than that recommended for the general population, or extending the dosing interval. Drug doses should be increased only after clinical examination and biochemical confirmation of stable liver function. Drugs with a narrow therapeutic index (including diazepam and warfarin) should also be used with caution in patients with cirrhosis, with low doses prescribed initially and up-titrated slowly as tolerated.[8]

Additional considerations in patients with cirrhosis

Electrolyte disturbances and the hepatorenal syndrome produced by frusemide appear to be the most frequent adverse drug reactions in patients with liver disease. Aminoglycosides can also increase a patient's susceptibility to renal failure if there is underlying cirrhosis.[5] Additionally, tissue responsiveness to the pharmacological action of some drugs may be modified, as evidenced by the increased susceptibility of the brain in patients with cirrhosis to the action of many psychoactive agents. Drugs may also interfere with the adaptive physiological process induced by liver disease. Angiotensin converting enzyme inhibitors (ACEIs) and non-steroidal anti-inflammatory drugs (NSAIDs) counteract the enhanced activity of the renin-angiotensin system in advanced liver disease, thereby generating a high risk of excessive hypotension or acute renal failure respectively.[9] Benzodiazepines and narcotic analgesics may increase the risk of hepatic encephalopathy in patients with cirrhosis and should be used with caution.

Prescribing in patients with abnormal liver function but no established cirrhosis

In patients with abnormal liver function but without evidence of cirrhosis there is no evidence to change prescribing behaviour. Liver function tests should be monitored when using medicines known to cause hepatic injury and the drug ceased in the event of deterioration of hepatic enzymes or evidence of acute liver failure.

Summary

There appears to be little evidence to change prescribing practice for patients with abnormal LFTs in the absence of decompensated cirrhosis. Idiosyncratic reactions causing drug-induced liver injury seem no more likely to occur in patients with pre-existing liver function abnormality or cirrhosis when compared to the general population. However, in patients who do have advanced liver disease there are complex pharmacokinetic and pharmacodynamic considerations. In these circumstances, medicines with predominant hepatic metabolism and/or excretion, particularly those with a narrow therapeutic index, must be used with caution.

Table 2 lists drugs commonly used in general practice that undergo extensive hepatic metabolism and/or have high hepatic extraction. These drugs need to be used with particular caution and drug doses need to be reduced to less than that recommended for the general population or the dosing interval extended.

Evidence based guidelines assisting clinicians with the dose adjustment of these medications in patients with advanced liver disease are not available, however resources such as the *Australian Medicines Handbook*[10] provides independent advice on prescribing in hepatic impairment. For this reason, use of these medicines must be done only in the context of careful clinical assessment and regular monitoring. Without a single and reliable measure of liver function it is important that clinicians have the skills to interpret test results and augment prescribing practices accordingly.

Practice points

- In the presence of decompensated cirrhosis, prescribing practices should be altered.
- Idiosyncratic drug reactions are equally common in patients with normal or abnormal liver function.
- In advanced liver disease, drugs with predominant hepatic metabolism and/or excretion, particularly those with a narrow therapeutic index, should be used with caution.

Authors

Emily Smith MBBS(Hons), is a gastroenterology registrar, Department of Gastroenterology, St Vincent's Hospital, Melbourne, Victoria. emily.smith@svhm.org.au

Paul Desmond MBBS, FRACP, is Director, Department of Gastroenterology, St Vincent's Hospital, Melbourne, Victoria.

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correspondence **afp@racgp.org.au**