Appendix 5: Hepatic impairment

Liver disease may alter the response to drugs. However, the hepatic reserve appears to be large and liver disease has to be severe before important changes in drug metabolism take place. The ability to eliminate a specific drug may or may not correlate with liver's synthetic capacity for substances such as albumin or clotting factors, which tends to decrease as hepatic function declines. Unlike renal disease, where estimates of renal function based on creatinine clearance correlate with parameters of drug elimination such as clearance and half-life, routine liver function tests do not reflect actual liver function but are rather markers of liver cellular damage.

The altered response to drugs in liver disease can include all or some of the following changes:

- Impaired intrinsic hepatic eliminating (metabolizing) capacity due to lack of or impaired function of hepatocytes.
- Impaired biliary elimination due to biliary obstruction or transport abnormalities (for example rifampicin is excreted in the bile unchanged and may accumulate in patients with intrahepatic or extrahepatic obstructive jaundice).
- Impaired hepatic blood flow due to surgical shunting, collateral circulation or poor perfusion with cirrhosis and portal hypertension.
- Altered volume of distribution of drugs due to increased extracellular fluid (ascites, oedema) and decreased muscle mass.
- Decreased protein binding and increased toxicity of drugs highly bound to proteins (for example phenytoin) due to impaired albumin production.
- Increased bioavailability through decreased first-pass metabolism.
- Decreased bioavailability due to malabsorption of fats in cholestatic liver disease.

In severe liver disease increased sensitivity to the effects of some drugs can further impair cerebral function and may precipitate *hepatic encephalopathy* (for example morphine). *Oedema* and *ascites* in chronic liver disease may be exacerbated by drugs that cause fluid retention (for example acetylsalicylic acid, ibuprofen, prednisolone, dexamethasone).

Usually drugs are metabolized without injury to the liver. A few drugs cause dose-related hepatotoxicity. However, most hepatotoxic reactions to drugs occur only in rare persons and are unpredictable. In patients with impaired liver function the dose-related hepatotoxic reaction may occur at lower doses whereas unpredictable reactions seem to occur more frequently. Both should be avoided.

Information to help prescribing in hepatic impairment is included in the following table. The table contains only those drugs that need dose adjustment. However, absence from the table does not automatically imply safety as for many drugs data about safety are absent; it is therefore important to also refer to the individual drug entries.

Table of drugs to be avoided or used with caution in liver disease

Drug	Comment
Abacavir	Avoid in moderate hepatic impairment unless essential; avoid in severe hepatic impairment
Acetylsalicylic acid	Avoid—increased risk of gastrointestinal bleeding
Alcuronium	Possibly slower onset, higher dose requirement and prolonged recovery time
Allopurinol	Reduce dose
Aluminium hydroxide	In patients with fluid retention, avoid antacids containing large amounts of sodium; also avoid those causing constipation (can precipitate coma)
Aminophylline	Reduce dose
Amitriptyline	Sedative effects increased (avoid in severe liver disease)
Amodiaquine	Avoid
Amoxicillin + Clavulanic acid	Monitor liver function in liver disease. Cholestatic jaundice reported either during or shortly after treatment; more common in patients over the age of 65 years and in males; duration of treatment should not usually exceed 14 days
Artemether + Lumefantrine	Caution in severe impairment; monitor ECG and plasma potassium
Azathioprine	May need dose reduction
Azithromycin	Avoid; jaundice reported
Bupivacaine	Avoid (or reduce dose) in severe liver disease
Carbamazepine	Metabolism impaired in advanced liver disease
Ceftriaxone	Reduce dose and monitor plasma concentration if both hepatic and severe renal impairment
Chloramphenicol	Avoid if possible—increased risk of bone-marrow depression; reduce dose and monitor plasma-chloramphenicol concentration
Chlorphenamine	Sedation inappropriate in severe liver disease—avoid
Chlorpromazine	Can precipitate coma; hepatotoxic
Ciclosporin	May need dose adjustment
Ciprofloxacin	Hepatic dysfunction reported
Clindamycin	Reduce dose
Clomifene	Avoid in severe liver disease
Clomipramine	Sedative effects increased (avoid in severe liver disease)
Clonazepam	Can precipitate coma
Cloxacillin	Cholestatic jaundice may occur up to several weeks after treatment has been stopped; administration for more than 2 weeks and increasing age are risk factors
Codeine	Avoid or reduce dose—may precipitate coma
Contraceptives, oral	Avoid in active liver disease and if history of pruritus or cholestasis during pregnancy
Cyclophosphamide	Reduce dose
Cytarabine	Reduce dose

Dacarbazine	Dose reduction may be required in mild to moderate liver disease; avoid if severe
Daunorubicin	Reduce dose
Diazepam	Can precipitate coma
Didanosine	Insufficient information but consider dose reduction
Doxorubicin	Reduce dose according to bilirubin concentration
Doxycycline	Avoid (or use with caution)
Efavirenz	In mild to moderate liver disease, monitor liver function; avoid in severe hepatic impairment
Enalapril	Closely monitor patients with impaired liver function
Ergometrine	Avoid in severe liver disease
Ergotamine	Avoid in severe liver disease—risk of toxicity increased
Erythromycin	May cause idiosyncratic hepatotoxicity
Ether, anaesthetic	Avoid
Ethinylestradiol	Avoid; *see also* Contraceptives, oral
Etoposide	Avoid in severe hepatic impairment
Fluconazole	Toxicity with related drugs
Fluorouracil	Caution advised
Fluphenazine	Can precipitate coma; hepatotoxic
Furosemide	Hypokalaemia may precipitate coma (use potassium-sparing diuretic to prevent this); increased risk of hypomagnesaemia in alcoholic cirrhosis
Glibenclamide	Increased risk of hypoglycaemia in severe liver disease; avoid or use small dose; can produce jaundice
Griseofulvin	Avoid in severe liver disease
Haloperidol	Can precipitate coma
Halothane	Avoid if history of unexplained pyrexia or jaundice following previous exposure to halothane
Heparin	Reduce dose in severe liver disease
Hydralazine	Reduce dose
Hydrochlorothiazide	Avoid in severe liver disease; hypokalaemia may precipitate coma (potassium-sparing diuretic can prevent this); increased risk of hypomagnesaemia in alcoholic cirrhosis
Ibuprofen	Increased risk of gastrointestinal bleeding and can cause fluid retention; avoid in severe liver disease
Indinavir	Reduce dose to 600 mg every 8 hours in mild to moderate hepatic impairment; not studied in severe impairment
Iopanoic acid	Avoid in severe hepatic disease
Isoniazid	Use with caution; monitor liver function regularly and particularly frequently in the first 2 months
Levonorgestrel	Avoid in active liver disease and if history of pruritus or cholestasis during pregnancy
Lidocaine	Avoid (or reduce dose) in severe liver disease
Lopinavir + Ritonavir	Avoid oral solution because of propylene glycol content; use capsules with caution in mild to moderate hepatic impairment and avoid in severe impairment

Magnesium hydroxide	Avoid in hepatic coma if risk of renal failure
Magnesium sulfate	Avoid in hepatic coma if risk of renal failure
Medroxyprogesterone	Avoid in active liver disease and if history of pruritus or cholestasis during pregnancy
Mefloquine	Avoid for prophylaxis in severe liver disease
Meglumine antimoniate	*see* Pentavalent antimony compounds
Mercaptopurine	May need dose reduction
Metformin	Withdraw if tissue hypoxia likely
Methotrexate	Dose-related toxicity—avoid in non-malignant conditions (for example, rheumatic disorders)
Methyldopa	Manufacturer advises caution in history of liver disease; avoid in active liver disease
Metoclopramide	Reduce dose
Metronidazole	In severe liver disease, reduce total daily dose to one-third and give once daily
Morphine	Avoid or reduce dose—may precipitate coma
Nalidixic acid	Hepatic dysfunction reported; partially conjugated in liver
Nelfinavir	No information available—manufacturer advises caution
Nevirapine	Caution in moderate hepatic impairment; avoid in severe hepatic impairment, *see also* section 6.5.2.2
Nifedipine	Reduce dose
Nitrofurantoin	Cholestatic jaundice and chronic active hepatitis reported
Norethisterone	Avoid in active liver disease and if history of pruritus or cholestasis during pregnancy
Ofloxacin	Hepatic dysfunction reported; reduce dose in severe liver disease
Paracetamol	Dose-related toxicity—avoid large doses
Pentavalent antimony compounds	Increased risk of liver damage and hepatic failure in pre-existing liver disease
Phenobarbital	May precipitate coma
Phenytoin	Reduce dose to avoid toxicity
Prednisolone	Adverse effects more common
Procainamide	Avoid or reduce dose
Procarbazine	Avoid in severe hepatic impairment
Promethazine	Avoid—may precipitate coma in severe liver disease; hepatotoxic
Propranolol	Reduce oral dose
Propylthiouracil	Reduce dose; *see also* section 18.8
Pyrazinamide	Avoid—idiosyncratic hepatotoxicity more common
Ranitidine	Increased risk of confusion; reduce dose
Rifampicin	Impaired elimination; may be increased risk of hepatotoxicity; avoid or do not exceed 8 mg/kg daily
Ritonavir	*See* Lopinavir + Ritonavir
Saquinavir	Plasma concentration possibly increased; manufacturer of gel-filled capsules advises caution in moderate hepatic impairment and avoid in severe impairment; manufacturer of

	capsules containing saquinavir mesilate advises caution in severe impairment
Sodium nitroprusside	Avoid in severe liver disease
Sodium valproate	*see* Valproic acid
Sulfadiazine	Avoid if severe
Sulfamethoxazole + Trimethoprim	Manufacturer advises avoid in severe liver disease
Suxamethonium	Prolonged apnoea may occur in severe liver disease due to reduced hepatic synthesis of plasma cholinesterase
Testosterone	Preferably avoid—possibility of dose-related toxicity and fluid retention
Theophylline	Reduce dose
Thiopental	Reduce dose for induction in severe liver disease
Valproic acid	Avoid if possible—hepatotoxicity and hepatic failure may occasionally occur (usually in first 6 months)
Verapamil	Reduce oral dose
Vinblastine	Dose reduction may be necessary
Vincristine	Dose reduction may be necessary
Warfarin	Avoid in severe liver disease, especially if prothrombin time already prolonged
Zidovudine	Accumulation may occur