- 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 are rare but tend to be unpredictable. In patients with impaired liver function, the dose-related hepatotoxic reaction may occur at lower doses and the 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.

Medicines to be avoided or used with caution in liver disease and type liver disease induced by the drug

Table 1.5 : Hepatic impairment and drugs

Medicine	Comment	Drug induced liver disease
Abacavir	Avoid in moderate hepatic impairment unless essential; avoid in severe hepatic impairment	-
Acetylsalicylic acid	Avoid in severe hepatic impairment increased risk of gastrointestinal bleeding	-
Allopurinol	Reduce dose	Acute Hepatocellular necrosis, Granulomatous hepatitis
Amitriptyline	Sedative effect increased (avoid in severe liver disease)	Acute hepatitis
Amlodipine	Half-life prolonged – may need dose reduction; consider initial dose of 2.5 mg	Cholestasis with hepatitis, chronic active hepatitis

Medicine	Comment	Drug induced liver disease
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	Cholestasis with hepatitis (clavulinic acid)
Artemether + lumefantrine	Caution in severe impairment – monitor ECG and plasma potassium	-
Aspirin	-	Acute Hepatocellular necrosis
Azathioprine	May need dose reduction	Cholestasis with hepatitis
Azithromycin	Avoid; jaundice reported	-
Bupivacaine	Avoid (or reduce dose) in severe liver disease	-
Carbamazepine	Metabolism impaired in advanced liver disease	Acute Hepatocellular necrosis, Chronic cholestasis, , Granulomatous hepatitis
Ceftriaxone	Reduce dose and monitor plasma concentration if both hepatic and severe renal impairment	-
Chlorambucil	Limited information available – consider dose reduction in severe hepatic impairment	-
Chloramphenicol	Avoid if possible – increased risk of bone marrow depression; reduce dose and monitor plasma chloramphenicol concentration	-
Chlorpheni-ramine	Sedation inappropriate in severe liver disease – avoid	-
Chlorpromazine	Can precipitate coma; hepatotoxic	Cholestasis with hepatitis, Chronic cholestasis, Granulomatous hepatitis
Ciclosporin	May need dose adjustment	Cholestasis without hepatitis
Clindamycin	Reduce dose	-
Clomifene	Avoid in severe liver disease	-
Clomipramine	Sedative effects increased; avoid in severe liver disease	Acute hepatitis
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	-

Medicine	Comment	Drug induced liver disease
Contraceptives, Oral	Avoid in active liver disease and if history of pruritus or cholestasis during pregnancy	-
Cyclophospha-mide	Reduce dose	Acute Hepatocellular necrosis
Cytarabine	Reduce dose	
Dacarbazine	Dose reduction may be required in mild to moderate liver disease; avoid if severe	-
Dantrolene	-	Acute Hepatocellular necrosis, Acute hepatitis, Chronic active hepatitis
Daunorubicin	Reduce dose	
Diazepam	Can precipitate coma	
Didanosine	Insufficient information but monitor for toxicity	Acute Hepatocellular necrosis
Doxorubicin	Reduce dose according to bilirubin concentration	-
Doxycycline	Avoid (or use with caution)	-
Efavirenz	In mild to moderate liver disease, monitor for dose related side-effects (for example, CNS effects) and monitor liver function; avoid in severe hepatic impairment	-
Enalapril	Closely monitor liver function in patients with hepatic impairment	Acute Hepatitis, Cholestasis with hepatitis
Ergometrine	Avoid in severe liver disease	
Erythromycin	May cause idiosyncratic hepatotoxicity	Cholestasis with hepatitis, Chronic cholestasis
Estradiol cypionate	Avoid	-
Ethinylestradiol	Avoid	-
Etoposide	Avoid in severe hepatic impairment	-
Fluconazole	Toxicity with related drugs	-
Fluorouracil	Caution advised; dose reduction may be required	-
Fluoxetine	Reduce dose or administer on alternate days	-
Fluphenazine	Can precipitate coma; hepatotoxic	-
Furosemide	Hypokalaemia may precipitate coma (use potassiumsparing 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	Cholestasis without hepatitis

Medicine	Comment	Drug induced liver disease
Griseofulvin	Avoid in severe liver disease	Cholestasis without hepatitis
Haloperidol	Can precipitate coma	-
Halothane	Avoid if history of unexplained pyrexia or jaundice following previous exposure to halothane	Acute Hepatocellular necrosis
Heparin	Reduce dose in severe liver disease	-
Hydralazine	Reduce dose	Granulomatous hepatitis
Hydrochloro-thiazide	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	Acute Hepatocellular necrosis
Indinavir	Increased risk of nephrolithiasis; reduce dose to 600 mg every 8 hours in mild to moderate hepatic impairment; not studied in severe impairment	-
Isoniazid	Use with caution; monitor liver function regularly and particularly frequently in the first 2 months;	Acute Hepatocellular necrosis, Acute hepatitis, Chronic active hepatitis
Labetalol	-	Acute Hepatocellular necrosis
Levonorgestrel	Caution in active liver disease and recurrent cholestatic jaundice	Cholestasis without hepatitis
Lidocaine	Avoid (or reduce dose) in severe liver disease	-
Lopinavir + ritonavir	Avoid oral solution because of propylene glycol content; avoid capsules in severe hepatic impairment	-
Magnesium hydroxide	Avoid in hepatic coma if risk of renal failure	-
Magnesium sulfate	Avoid in hepatic coma if risk of renal failure	-
Medroxy-progesterone acetate	Avoid in active liver disease and if history of pruritus during pregnancy	-
Mefloquine	Avoid for prophylaxis in severe liver disease	-
Mercaptopurine	May need dose reduction	-
Metformin	Withdraw if tissue hypoxia likely—manufacturers advise avoid	-
Methadone	Avoid or reduce dose—may precipitate coma	-

Medicine	Comment	Drug induced liver disease
Methotrexate	Dose-related toxicity; avoid in non-malignant conditions (for example, rheumatic disorders); avoid for all indications in severe hepatic impairment	-
Methyldopa	Manufacturer advises caution in history of liver disease; avoid in active liver disease	Acute Hepatocellular necrosis, Acute hepatitis, Granulomatous hepatitis
Metoclopramide	Reduce dose	-
Metronidazole	In severe liver disease, reduce total daily dose to one third and give once daily	-
Monoamine oxidase inhibitors (MAOIs)	-	Acute hepatocellular necrosis, Acute hepatitis
Morphine	Avoid or reduce dose—may precipitate coma	-
Nelfinavir	No information available; manufacturer advises caution	-
Nevirapine	Caution in moderate hepatic impairment; avoid in severe hepatic impairment	-
Nifedipine	Reduce dose in severe liver disease	Acute hepatitis
Nitrofurantoin	Cholestatic jaundice and chronic active hepatitis reported	Cholestasis with hepatitis, Chronic active hepatitis, Granulomatous hepatitis
Norethisterone	Avoid in active liver disease and if history of pruritus or cholestasis during pregnancy	Cholestasis without hepatitis
Ofloxacin	Hepatic dysfunction reported; reduce dose in severe liver disease	-
Paracetamol	Dose-related toxicity—avoid large doses	Acute Hepatocellular necrosis, chronic active hepatitis
Pentavalent antimony compound	Increased risk of liver damage and hepatic failure in pre-existing liver disease	-
Phenobarbital	May precipitate coma	-
Phenytoin	Reduce dose to avoid toxicity	Acute hepatitis, Cholestasis with hepatitis, chronic active hepatitis, Chronic cholestasis, Granulomatous hepatitis
Prednisolone	Adverse effects more common	-

Medicine	Comment	Drug induced liver disease
Procainamide	Avoid or reduce dose	Granulomatous hepatitis
Procarbazine	Avoid in severe hepatic impairment	-
Promethazine	Avoid—may precipitate coma in severe liver disease; hepatotoxic	-
Propranolol	Reduce oral dose	-
Propylthiouracil	Reduce dose;	-
Pyrazinamide	Monitor hepatic function—idiosyncratic hepatotoxicity more common; avoid in severe hepatic impairment;	Acute hepatitis
Pyrimethamine	Use with caution	-
Ranitidine	Increased risk of confusion; reduce dose	Cholestasis with hepatitis
Ribavirin	Avoid in severe hepatic dysfunction or decompensated cirrhosis	-
Rifampicin	Impaired elimination; monitor liver function; avoid or do not exceed 8 mg/kg daily	Acute hepatitis
Ritonavir	See Lopinavir + ritonavir	-
Saquinavir	Manufacturer advises caution in moderate hepatic impairment; avoid in severe impairment	-
Simvastatin	Avoid in active liver disease or unexplained persistent elevations in serum transaminases	-
Sodium nitroprusside	Avoid in severe liver disease	-
Sulfadiazine	Avoid if severe	-
Sulfamethoxazole + trimethoprim	Manufacturer advises avoid in severe liver disease	-
Sulphonamides	-	Acute Hepatocellular necrosis, Acute hepatitis, Cholestasis with hepatitis, chronic active hepatitis, Granulomatous hepatitis
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	-
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)	Acute Hepatocellular necrosis
Verapamil	Reduce oral dose	-

Medicine	Comment	Drug induced liver disease
Vinblastine	Dose reduction may be necessary	-
Vincristine	Dose reduction may be necessary	-
Warfarin	Avoid in severe liver disease, especially if prothrombin time already prolonged	Cholestasis without hepatitis
Zidovudine	Accumulation may occur	-