Drugs that damage the liver

Alison M Brind

Abstract

Drugs that damage the liver account for 9.5% of all suspected adverse drug reactions (ADRs), are the main cause of fatal ADRs and are the most common reason for withdrawal of drugs from the market. Pre-market surveillance detects common ADRs, but those seen in clinical practice are rare (1 in 10,000–100,000). Their recognition depends on individual reports and post market surveillance. In the UK, the yellow card scheme is used to report all suspected ADRs with new drugs and serious ADRs with established drugs. Both under-reporting and over-reporting occur. Information on hepatotoxicity, therefore, is neither systematic or comprehensive. The liver is particularly affected as it is the central metabolizing organ through which all foreign compounds pass. Injury may be a direct toxic effect or immunological reaction to either the drug or an active metabolite formed by bio-activation (it was reported that for 62% of withdrawn drugs it is the metabolite that is toxic). Any type of liver injury can be reproduced by drugs and any drug can produce different types of liver injury. Injury may be acute or chronic and there can be adaptation to injurious effects with a transient increase in liver function in patients that have significant ongoing injury. Many factors interact to lead to injury and there is considerable variation in susceptibility which may be inherited and acquired. This contribution focuses on general principles of drug-induced liver disease. Information on specific ADRs can be obtained from the *British National Formulary*, drug datasheets and databases.

Keywords adverse drug reactions; cholestatic hepatitis; drug induced liver injury; drug metabolism; paracetamol toxicity; steatosis

What's new?

- Increase in non-accidental paracetamol toxicity
- Increase in herbal and alternative medicine use and, therefore, associated liver injury
- Increased understanding of biliary transporters and mechanism of cholestasis
- Increased understanding of variability in drug metabolism in terms of bioactivation, detoxification and oxidation

Mechanisms of liver injury

Direct effect vs immunological reactions: drugs or their metabolites may have a direct toxic effect or may induce an immune reaction to cellular proteins (e.g. by altering them so that they become autoantigens, by binding to proteins to induce neoantigens). Direct effects lead to predictable, dose-dependent toxicity. Immune reactions are dose independent, occur rapidly (often within 1–5 days) and are associated with hypersensitivity phenomena such as fever, rash and eosinophilia. Table 1 provides a summary of effects that drugs can have on the liver.

Alison M Brind *MD FRCP is Consultant Physician in the North Staffordshire NHS Trust and Visiting Consultant in the Liver Unit at Queen Elizabeth Hospital, Birmingham, UK. Competing interests: none declared.*

Necrosis – may be from direct toxicity or immunological. Cellular disintegration is caused by injury to plasma membranes and organelles. Apoptosis (programmed cell death) is also seen in drug-induced liver injury. Necrosis may predominantly involve a particular liver zone because the enzymes involved in drug metabolism are often zonally distributed (cytochrome P4502E1, involved in paracetamol metabolism, is predominantly in zone 3 – centrilobular) or because toxicity depends on the oxygen gradient of liver zones. Non-zonal necrosis is usually immunologically mediated. The clinical manifestations of necrosis depend on the extent and duration. Recovery after submassive zonal necrosis occurs without significant scarring, but non-zonal necrosis may lead to nodular scarring.

Associated inflammation varies; there is often little inflammatory change in acute necrosis, but some drugs are associated with characteristic patterns of inflammation:

- phenytoin – pseudomononucleosis type
- diclofenac and isoniazid – acute hepatitis type
- allopurinol, sulphonamides and phenybutazone – granulomatous type.

A chronic necro-inflammatory reaction occurs with some drugs (such as diclofenac, ecstasy, minocycline, dihydralazine, lisinopril, trazadone and dantrolene) that resembles autoimmune chronic hepatitis and may be associated with positive autoantibodies and hyperglobulinaemia.

Steatosis – certain drugs are associated with accumulation of fat droplets in hepatocytes. Microvesicular steatosis is seen with tetracycline, valproate, aspirin overdose and nucleoside analogues, and results from a direct effect on mitochrondria and β-oxidation. Macrovesicular steatosis corresponds to triglyceride accumulation due to defects in lipoprotein metabolism, damage to plasma membrane or increased lipid delivery to hepatocytes consequent on increased synthesis or mobilization. Some drugs (e.g. minocycline) produce both microvesicular and macrovesicular steatosis. Chronic steatosis with Mallory bodies (usually seen in alcoholic liver disease) is seen with nifedipine, corticosteroids and tamoxifen. Phospholipidosis (phospholipids accumulated in lysosomes as a result of inhibition of phospholipases) is seen with thioridazine and chlorpheniramine. Both conditions can occur with some drugs (e.g. amiodarone).

There may be accompanying necro-inflammation and/or fibrosis (pseudoalcoholic liver disease), which may progress to cirrhosis (amiodarone and tamoxifen), or no inflammation (corticosteroids).

Liver damage by drugs

Injury	Mechanism	Clinical pattern	Biochemical pattern *BIL*	*AST/ALT*	*ALP*	Example
Necrosis						
• Zone 3 • Zone 1	Drug/metabolite – direct cytotoxicity or immunotoxicity to autoantigen or neo-antigen leads to	Acute – fulminant hepatic failure	+	10–100x	1–3x	Paracetamol overdose, halothane, amanita, ferrous salt overdose
• Non-zonal • Massive	injury to plasma membrane and organelles; zone	Subacute necrosis – slow-onset liver failure	+	5–25x	1–3x	Phenytoin, diclofenac
• Necro-inflammation	depends on enzyme producing toxic metabolite	Acute 'hepatitis'	+++	10–100x	1–5x	Isoniazid, diclofenac, dantrolene
		Chronic necrosis with fibrosis	+/++	3–50x	1–3x	Nitrofurantoin, methyldopa, diclofenac
		Chronic autoimmune hepatitis	+/++	3–10x	1–3x	Minocycline, lisinopril
Steatosis						
• Microvesicular	Inhibtion of mitochrondrial β-oxidation	Reye's syndrome	+	5–2x	1–3x	Tetracycline, aspirin, valproate, nucleoside analogues
• Macrovesicular	Decreased hepatocyte lipoprotein secretion	Acute alcoholic hepatitis	+++	1–5x	1–3x	Methotrexate, amiodarone,
		Chronic steatohepatitis with Mallory bodies	+/++	1–5x	Vx	nifedipine, glucocorticoids, tamoxifen
• Phospholipidosis	Accumulation of phospholipids by inhibition of phospholipases or binding to phospholipases	Chronic steatohepatitis with phospholipidosis	+++	1–5x	1–3x	Chlorpheniramine, thioridazine
		Chronic steatohepatitis and cirrhosis	+/++	1–5x	Vx	Amiodarone
Cholestasis						
• Pure	Selected interference with bile formation and flow	Cholestatic jaundice	+/+++	1–5x	1–3x	Anabolic and contraceptive steroids, ciclosporin, fucidin
• Cholestatic	Toxin – cytotoxic or immune-mediated injury to bile duct	Acute cholestatic hepatitis	+/+++	1–10x	> 3x	Flucloxacillin, co-amoxiclav, erythromycin, chlorpromazine
		Chronic vanishing bile ducts/primary biliary cirrhosis type				Chlorpromazine, flucloxacillin
• Mixed cholestatic/ hepatocellular	Toxin – cytotoxic or immune-mediated injury to bile duct and hepatocytes	Cholestatic/hepatocellular	+/++	10–100x	1–3x	Phenytoin, sulphonamides

(continued on next page)

Liver damage by drugs (Continued)

Injury	Mechanism	Clinical pattern	Biochemical pattern			Example
			BIL	*AST/ALT*	*ALP*	
Vascular lesions						
• Hepatic vein thrombosis	Thrombogenic effects	Budd–Chiari syndrome – congestive hepatopathy	+/+++	2–20x	Vx	Contraceptive steroids
• Nodular regenerative hyperplasia	Toxic damage to endothelium portal vein	Portal hypertension	+	1–3x	Vx	Anabolic and contraceptive steroids, oncotherapy, toxic oil
• Veno-occlusive disease	Toxic damage to endothelium and zone 3 hepatocytes	Congestive hepatopathy	Vx	Vx	Vx	Pyrrolidine alkaloids, azathioprine, oncotherapy
• Peliosis hepatic, sinusoidal dilatation	Toxic damage to endothelium and sinusoid	Congestive hepatopathy	Vx	Vx	Vx	Azathioprine, oncotherapy, vitamin A
Neoplasia						
• Hepatocellular carcinoma and adenoma	DNA and RNA damage		Vx	Vx	Vx	Anabolic and contraceptive steroids

V, variable; BIL, bilirubin; AST, aspartate transaminase; ALP, alkaline phosphatase; ALT, alanine aminotransferase.

Table 1

Cholestasis – patients with cholestasis have pruritus, pale stools and bilirubin in urine. The mechanisms are not clearly understood but involve interference in the function of one of the ATP binding superfamily of canulicular transporters such as BSEP, MDR3 and MRP2. Such interference in function may lead to benign cholestasis with little or no liver injury but selective interference in bile formation and flow (e.g. oestrogens and cyclosporin), or an immunogenic or direct toxic effect on biliary canaliculi of drug or accumulated toxins consequent upon drug induced inhibition of their secretion. In some cases, there is overlap with acute hepatocellular injury, producing 'mixed hepatitis'. Cholestasis may become chronic and can be associated with ongoing loss of bile ducts (ductopenia), even after discontinuation of the drug (e.g. chlorpromazine, tolbutamide, flucloxacillin).

Vascular/sinusoidal lesions – drugs may affect the vascular endothelium, liver sinusoidal structures or clotting system. Hepatic vein thrombosis may occur in predisposed oral contraceptive users, often as a result of latent myeloproliferative disorders. In veno-occlusive disease and nodular regenerative hyperplasia, there is direct acute or chronic Injury to venular endothelium and zone 3 hepatocytes. Injury to sinusoidal supporting structures leads to peliosis hepatis, sinusoidal dilatation or hepatoportal sclerosis (a toxic effect of vitamin A).

Neoplasia – induction of neoplasia requires prolonged drug administration. Carcinogenesis is induced by DNA damage by electrophilic metabolites leading to alkylation, acylation or addition of heterocyclic radicals.

Factors affecting susceptibility (Table 2):

- **Age** – toxicity is more common at the extremes of age, partly because of increased chances of drug interactions in the elderly and significant co-morbidities. There are also classical age-dependent disorders (e.g. Reye's syndrome – childhood aspirin-induced microvesicular steatosis).
- **Gender** – females are more susceptible to flucloxacillin, methyldopa and nitrofurantoin, and males to azathioprine and co-amoxiclav cholestatic hepatitis
- **Nutritional state** – depletion of glutathione by fasting, pregnancy or alcohol increases the risks of paracetamol and intravenous tetracycline toxicity in pregnancy.
- **Chronic alcohol abuse** – affects toxicity by enzyme induction and common pathways of injury such as steatosis (increased susceptibility to methotrexate).
- **Systemic disease** – (particularly hyperthyroidism in halothane hepatitis) may predispose to drug damage.
- **Detoxification** – paracetamol is detoxified by glucuronidation, sulfation and conjugation with glutathione and functional or genetic changes in UDP-glucuronosyltransferases (UGT) sulfotransferases and glutathione–S-transferases affect paracetamol toxicity. It has been suggested that individuals with Gilbert's syndrome caused by mutation in UGT1A1 may be more susceptible. In addition, the risk of hepatotoxicity is increased by inactive N-acetyltransferase (sulphonamide and hydralazine), deficiency of functional sulfoxidation (chlorpromazine).
- **Oxidation** – metabolism by cytochrome P450 (CYP) is important to injury and susceptibility because of common polymorphysims in

Factors affecting susceptibility to drug-induced liver disease

Factor	Drug
Age > 60 years	Isoniazid, nitrofurantoin
Children	Valproic acid, salicyclates
Gender	
• Women	Methyldopa, nitrofurantoin, flucloxacillin
• Men	Azathioprine, co-amoxiclav
Obesity	Halothane
Fasting/malnutrition	Paracetamol
Pregnancy	Paracetamol and tetracycline
Obesity and diabetes	Drugs causing steatohepatitis
HIV infection	Co-trimoxazole and sulphonamides
Chronic alcohol abuse	Paracetamol and methotrexate
Other drugs	
• Enzyme inducers	Rifampicin and isoniazid
• Enzyme inhibitors	Oestrogens
Metabolic enzyme polymorphisms	
• Bioactivation	
• Detoxification	
N-acetyltransferase	Sulphonamides, dihydralazine
Glucuronosyltransferase	Paracetamol
Sulfoxidation	Chlorpromazine
Glutathione synthetase	Paracetamol
Glutathione-S-transferase	Tacrine, paracetamol
• Oxidation	
CYP2D6 or CYP2C19	Perhexilene and barbiturates phenytoin, carbamazepine and sulphonamides
HLA polymorphisms	Halothane, tricyclic antidepressants, diclofenac, nitrofurantoin and chlorpromazine
Biliary transporters	Rifampicin, glibenclamide and oestrogens

Table 2

P450 enzymes and common prescription of P450 inducers (phenytoin, carbamazepine and rifampicin) or inhibitors (erythromycin, paroxetine and omeprazole). Functional genetic polymorphisms in P450 and other drug-metabolizing enzymes are important in susceptibility to some drugs. P4502D6 and P4502C19 (perhexilene and hydralazine) It is assumed that other polymorphisms affecting as yet uncharacterized detoxification enzymes will explain the known familial predisposition to hepatic drug reactions.

- **Biliary transport** – see section on cholestasis.
- **Immune response** – immune reactions may be influenced by HLA polymorphisms. In addition, certain immune hepatitis is associated with antibodies to certain P450 enzymes (P5402C9 and 1A2).

Considerable research is ongoing into the genetic basis of drug-Induced liver injury, which are most likely to be multfactorial.

Diagnosis

Diagnosis of drug-induced liver injury (Table 3) depends on the history of a pattern of liver injury characteristic for a prescribed drug and on the exclusion of other causes. International consensus criteria have been developed in which different features are scored to aid diagnosis. Drug-induced liver disease may be suspected in patients with symptomatic liver disease and those with asymptomatic elevations in liver function tests (LFTs). It is more common in patients over 50 years of age who are taking multiple drugs.

Abnormalities are commonly detected 5–90 days after drug administration, but can occur up to 5 weeks post-withdrawal or after long term use. Reaction on re-challenge may be immediate. Immunological reactions are often accompanied by fever (hepatitis associated with fever is more likely to be drug related than a viral infection), rash and eosinophilia. Recovery (defined as >50% decrease in abnormal LFTs) on withdrawal of the suspected drug supports the diagnosis, but the speed of recovery depends on the type of injury. Acute hepatocellular injury may take up to 2 months; cholestatic injury may take up to 6 months, and may worsen up to 2 weeks post-withdrawal or, rarely, is irreversible. Re-challenge reactions give a positive diagnosis but are not usually required and can be dangerous in acute-type hepatocellular reactions accompanied by features of hypersensitivity.

Diagnosis depends on the exclusion of other causes of liver dysfunction. It is important to take a good history to exclude alcoholic liver disease or structural obstructive jaundice. An episode of hypotension may cause ischaemic hepatitis and right heart failure may cause hepatic congestion. Diabetes predisposes to steatosis/steatohepatitis. Serum viral markers, autoantibody detection and iron and copper studies should also be undertaken. Ultrasonography should be performed to exclude structural disease. Liver biopsy may be useful if the diagnosis is uncertain, to eliminate other causes or show characteristic drug lesions. Biopsy may also be helpful In characterizing lesions with drugs not yet recognized as hepatotoxins, In determining the severity of lesions when LFTs do not reflect the extent of damage and In determining the prognosis of chronic liver Injury such as vanishing bile ducts. Some drug reactions are associated with specific autoantibodies or drug antibodies, but other allergy testing is not usually helpful.

Stages in the diagnosis of drug-induced liver disease

- History – drug, clinical
- Characterization of injury and comparison with known ADRs
- Temporal relationships – onset 5–90 days
- Withdrawal and normalization
- Extrahepatic manifestations – fever, rash, eosinophilia, cytopenia, arthralgia
- Exclusion of alternative cause
- ?Re-challenge
- ?Liver biopsy
- ?Specific antibody/leucocyte tests/allergy testing

Table 3

Management

Prevention, early recognition and prompt withdrawal of likely offending drugs are the most important elements. Sometimes, withdrawal does not prevent progression. Non-essential drugs should be withdrawn if liver enzymes become elevated above the normal range. Essential drugs may be reintroduced cautiously, depending on the known natural history of the ADR. There is no evidence basis for the use of corticosteroids or ursodeoxycholic acid. Management is generally supportive until recovery. If liver failure supervenes, transplantation is required.

Changes in the pattern of drug-induced liver injury

There is increasing incidence of non-accidental paracetamol induced acute liver disease and failure in patients taking often not more than the therapeutic recommended dose. Many have increased risk of paracetamol toxicty, such as alcohol abuse, or have taken paracetamol plus paracetamol combination analgesics together.

Herbal or alternative remedies are becoming a common cause of drug-induced liver disease but information on toxicity is fragmented relying on individual case reports and compounded by variations in specific herbal products. ◆

FURTHER READING

Larrey D. Drug-induced liver disease. *J Hepatol* 2000; **32**(Suppl. 1): 77–88.

Stickel F, Patsenker E, Schuppan D. Herbal hepatotoxicity. *J Hepatol* 2005; **43:** 901–10.

Watkins P B, Seef L B. Drug-induced liver injury: summary of a single topic clinical research committee. *Hepatology* 2006; **43:** 618–31.

Zimmerman H J. *Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver*. 2nd ed. Philadelphia: Lippincott Williams and Wilkins, 1999.

