Drugs and the liver

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This article discusses the classification, epidemiology, mechanisms and pathology of drug-induced liver disease. A number of specific examples involving commonly used drugs are discussed.

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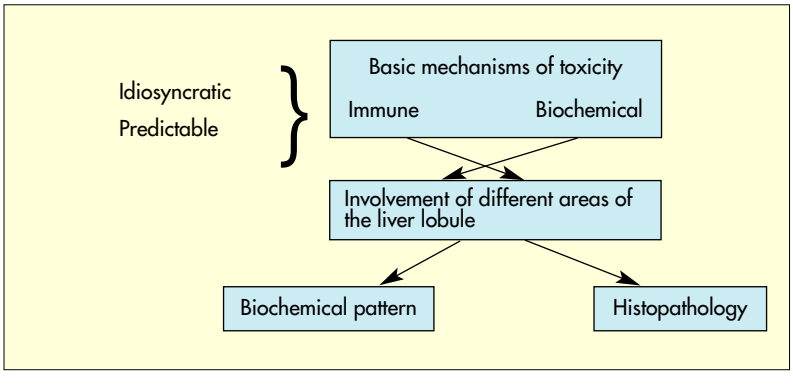
Drug-induced liver injury is one of the most common causes of hepatic failure leading to death or liver transplantation. Hepatotoxicity is the leading cause for drug withdrawal from clinical practice (Larrey, 2002). The whole spectrum of liver disease may be observed, although an acute hepatitis is the most common.

The first part of this review discusses the different mechanisms by which drugs cause liver injury, and the second part explores some of the common problems encountered in clinical practice.

EPIDEMIOLOGY OF ADVERSE DRUG REACTIONS AFFECTING THE LIVER

For any given drug, only a tiny minority of cases will develop serious problems. In clinical trials where only a few thousand patients are involved it is therefore not surprising that these problems are often not identified. This means that most severe hepatotoxic side effects of drugs are only identified in post-marketing surveillance. It is therefore crucial to report suspected hepatotoxic reactions in newly marketed drugs via the yellow card system in the *British National Formulary* (British Medical Association and Royal Pharmaceutical Press of Great Britain, 2004) or directly to the Medicines Control Agency (http://www.mca.gov.uk/home.htm).

Figure 1. Overview of drug-induced hepatotoxicity. Injury may be immune or biochemical and will involve different areas of the liver according to the drug. This in turn will produce the particular biochemical and histopathological pattern.



FACTORS DETERMINING INDIVIDUAL SUSCEPTIBILITY

There is a complex interplay between drug and patient. Drugs differ in their route of elimination, the enzymes involved in their metabolism and the mechanism of hepatotoxicity. Individuals are just that.

Certain groups are more susceptible than others. Children are more prone to microvesicular steatosis in response to salicylates or valproic acid, older people are more prone to isoniazid toxicity. Gender is important (in general females have a higher incidence of adverse drug reactions), as are nutritional status, pregnancy, chronic alcohol abuse, pre-existing liver disease and prior drug therapy. Probably more important than currently recognized are genetic polymorphisms of key enzymes in drug metabolism (especially cytochrome p450 enzymes) and immune recognition (e.g. human leukocyte antigen (HLA) type). Multiple factors multiply the risks by providing extra pressure on the molecular homeostasis of the liver. For example obese individuals with large amounts of fat stored in the liver will have more trouble from lipid peroxidation if exposed to oxidative stress.

MECHANISMS OF LIVER INJURY

Toxic compounds affect the liver in two main ways: by generating an immune response or by directly interfering with cellular biochemistry. In practice there is often much overlap between the two processes. The liver is anatomically positioned to receive these compounds via the portal circulation. The particular region of the liver lobule involved determines the clinical, biochemical and histopathological picture (*Figure 1*). The route taken by a drug as it enters the liver is outlined in *Figure 2*.

Drug bound to protein in the blood enters the hepatic sinusoids either via the portal or systemic circulations and from here enters the space of Disse by passive diffusion. Entry of the drug into the hepatocyte is either by active transport via dedicated transporters or passive diffusion,

and it is here where phases 1 and 2 of metabolism take place. Metabolites are then either returned to the space of Disse and enter the circulation where they are excreted by the kidneys or enter the biliary system. Clearly there are multiple cells and cellular organelles in the process with which to interact and this reflects the range of pathology. The pattern of damage may be zonal, usually around the central veins because the perivenular hepatocytes contain higher concentrations of drug-metabolizing enzymes (*Figure 3*), although idiosyncratic drug reactions tend to be diffuse.

Immune-mediated injury

Drugs are metabolized to peptides and other small molecules that covalently bind to proteins within the liver, forming hapten–carrier conjugates. Presentation by major histocompatibility complex (MHC) class 1 on the surface of liver cells leads to sensitization of T lymphocytes. These then recognize and attack the affected cells by cytokine- and porin-mediated mechanisms. The action of tumour necrosis factor (TNF) via the Fas ligand triggers caspase pathways and triggers apoptosis. Differences in individuals relating to HLA haplotypes and other steps in the immune recognition and effector arms are clearly important. In some cases there may be features of hypersensitivity with rash, fever, eosinophilia and infiltration of inflammatory cells into the liver (*Figure 4*).

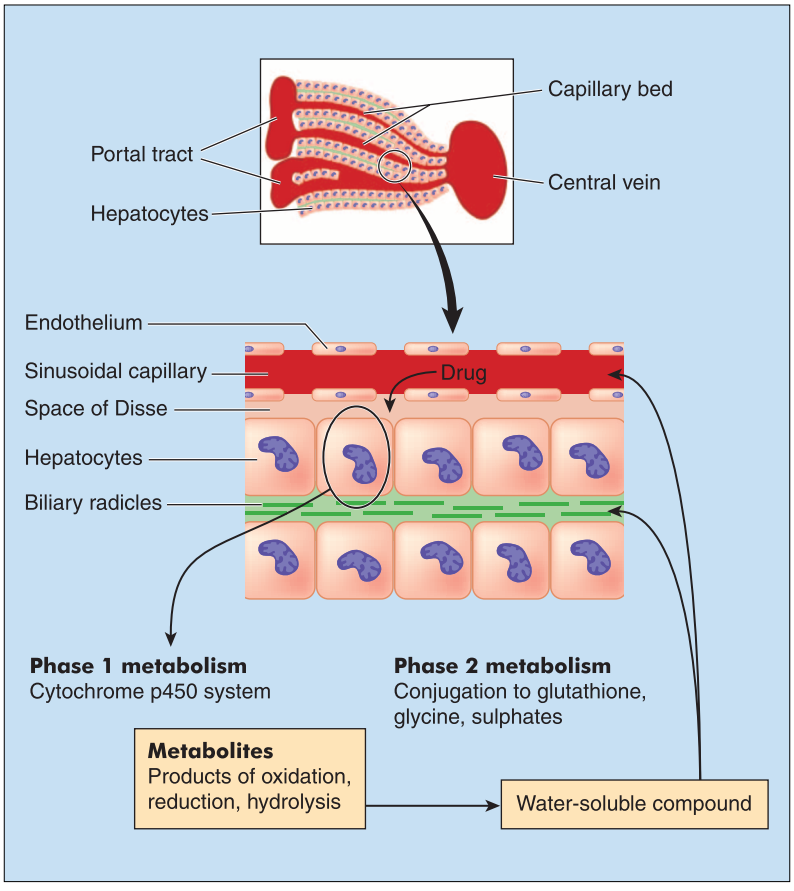
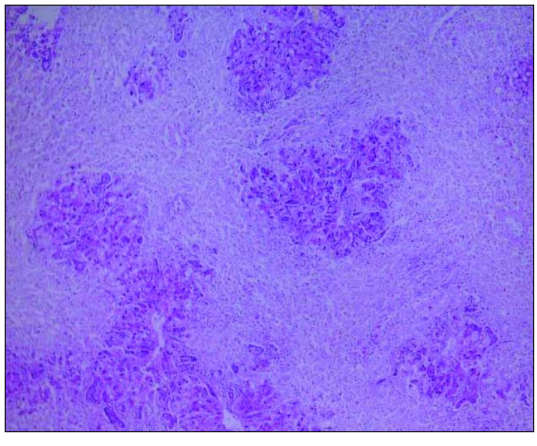


Figure 2. Passage of drug through the liver. Protein-bound drug enters the liver via the portal or systemic circulation and passes into the sinusoidal capillaries. Diffusion of drug occurs into the space of Disse, and from here it passes into the hepatocyte either by active transport or passive diffusion. Metabolism occurs inside the hepatocyte at the end of which the products are either transported into the bile, or return to the circulation for eventual excretion by the kidney.

Biochemical injury

Drugs and other exogenous compounds are biotransformed by the liver in two phases as described above. Either the drug itself or the metabolites generated from these processes can have a number of biochemical consequences (e.g. covalent binding, glutathione depletion and redox changes, oxidative stress leading to lipid peroxidation and DNA damage), which lead to intracellular stress. If severe enough this may disrupt the balance of factors favouring survival of the cell. Any organelle may be affected but the end result is the release of various mediators (e.g. caspases and transcription factors such as

Figure 3. A fatal case of paracetamol-induced liver damage characterized by confluent perivenular necrosis. Darker staining areas of residual liver stand out.



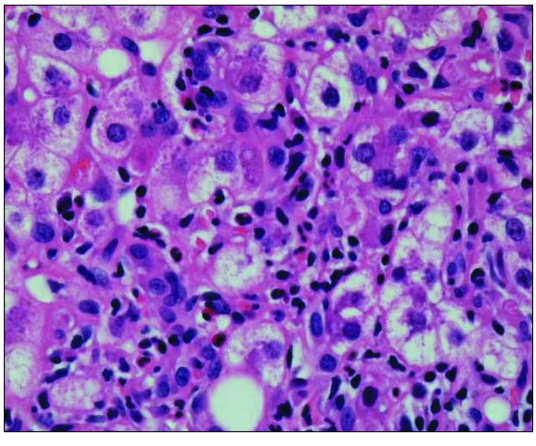


Figure 4. A cholestatic hepatitis caused by erythromycin. There is a combination of hepatocyte and bile duct damage and regeneration associated with cholestasis, and an inflammatory infiltrate rich in eosinophils and plasma cells.

Bim and Bmf), which trigger the release of mitochondrial proteins into the cytosol leading to necrosis or apoptosis. These processes are affected by variability between individuals in metabolism, transport, defence, regeneration and the pro death/pro survival balance of the hepatocyte.

Oxidative stress results from exposure to increased levels of reactive oxygen species, either as a result of enhanced production or reduced removal. The main source of these reactive oxygen species are the mitochondria, but also the microsomal p450 system (notably CYP2E1), peroxisomal oxidases, and iron and copper overload. Oxidative stress leads to lipid peroxidation, protein thiol oxidation, DNA oxidation and changes in the glutathione redox buffer. This in turns activates redox-sensitive kinases and transcription factors (e.g. AP1, NFkB, p53), which upregulate cytokines, chemokines and adhesion molecules, producing inflammation, necrosis and apoptosis.

INDIVIDUALS WITH PRE-EXISTING LIVER DISEASE

Pre-existing liver disease may alter the metabolism of drugs. For example, in alcoholic patients, paracetamol may induce liver injury even in relatively small amounts. However, most drug reactions are idiosyncratic and so an increased incidence of toxicity does not necessarily follow. Pre-existing abnormalities in liver biochemistry resulting from underlying disease may be falsely attributed to the drug. In an epidemiological study of patients taking statins, those with abnormal liver biochemistry at baseline showed no significant difference from a matched group of individuals with abnormal blood tests who were not given a statin (Chalasani et al, 2004). If toxicity does occur in these patients it may lead to worse consequences because of the lack of hepatic reserve, so prescribing of drugs in patients with advanced liver disease should be kept to a minimum, especially in patients with decompensated liver disease.

TABLE 1.
Biochemical classification of drug-induced injury

Type	Blood biochemistry	Other features	Recovery
Acute hepatocellular injury	ALT>2xULN or ALT/ALP >5	Most common type includes: necrosis, hepatitis, steatosis (macro- or microvesicular)	1–3 months after discontinuation If leading to liver failure, 90% mortality without OLT
Acute cholestatic injury	ALP>2xULN	Pure (bland) cholestasis ALT normal pruritis and jaundice	
or	ALT/ALP <2	Cholestatic hepatitis Unwell, pain, may mimic cholangitis, biliary obstruction. Hypersensitivity features	May continue up to 3 months after withdrawal Can become chronic if lots of bile duct injury
Mixed pattern	ALT/ALP 2–5	Hepatocellular/ cholestatic mix. Includes granulomatous reactions	

From Benichou (1990). ALP = alkaline phosphatase; ALT = alanine transaminase; OLT = orthotopic liver transplant; ULN = upper limit of normal

BIOCHEMICAL AND HISTOPATHOLOGICAL PATTERNS OF DRUG-INDUCED LIVER INJURY

Drug reactions can be classified either by the pattern of biochemical injury they cause or by the histological insult seen on liver biopsy (or at post mortem). In everyday practice, particularly for the non-hepatologist, the former is the more immediately useful and by consensus (Benichou, 1990) they are usually classified as in *Table 1*.

HISTOPATHOLOGICAL FEATURES

Liver biopsy is important for characterizing the pattern of drug-induced injury as well as helping to rule out other causes of abnormal liver biochemistry. The whole spectrum of liver disease may be observed. Some examples of drugs and the morphological changes typically associated with them are shown in *Table 2*. As a consequence of this, there is almost no pattern of liver injury that is diagnostic of a drug cause. There are, however, features which do suggest this.

The commonest is a cholestatic hepatitis where there is a combination of hepatocyte and bile duct damage associated with cholestasis, and a conspicuous eosinophil and plasma cell infiltrate (*Figure 4*). Hepatocellular damage occurs as a result of a direct effect leading to cell dysfunction, such as is seen with isoniazid, diclofenac and lovastatin. Cholestasis results from injury to the canalicular membrane and

TABLE 2.
Morphological changes observed at liver biopsy

Type of reaction	Acute
Hepatocellular injury	Paracetamol, phenytoin, isoniazid
Cholestasis	Chlorpromazine, erythromycin
Granulomatous	Diltiazem, phenylbutazone
Neoplastic	Vinyl chloride, sex hormones
Steatosis	Amiodarone, phenothiazines, nitrofurantoin
Vascular	Ergot, cocaine

transporters by drugs such as chlorpromazine, and oestrogens. Granulomatous reactions result from macrophage infiltration and are seen with many drugs, a common one being diltiazem. Steatohepatitis may occur with amiodarone, tamoxifen and following industrial exposure to petrochemicals (*Figure 5*). Some drugs such as methyldopa and minocycline may directly trigger an autoimmune reaction. Vascular ischaemic or hypoxic injury may also be induced. Drugs such as methotrexate, when taken long term, can lead to fibrosis and eventually cirrhosis (*Figure 6*). Finally drugs may be oncogenic such as sex hormones and vinyl chloride (*Figure 7*).

DIAGNOSIS AND TREATMENT OF DRUG-INDUCED HEPATOTOXICITY

In general there are no markers for drug-induced liver injury. The diagnosis relies mainly on circumstantial evidence and a high index of clinical suspicion. Attempts have been made to construct scoring systems to give a range of likelihoods that a drug under suspicion is the culprit. Probably the best example of this is the RUCAM (Roussel Uclaf Causality Assessment Method) system (Lucena et al, 2001), which assigns points based on clinical and chronological criteria.

Most drugs have been started in the 3 months leading up to the diagnosis of liver injury, although longer durations are not unknown. If liver biochemistry improves after drug withdrawal, particularly within the first week, then this is highly suggestive. Relapse after (accidental) re-challenge adds further weight.

From a clinical point of view it is important to exclude other causes of abnormal liver biochemistry, such as those caused by viruses, alcohol, autoimmunity, Wilson's disease, biliary obstruction, and previous hepatic or biliary disease. Positive criteria include older age groups, polypharmacy, known hepatotoxic drugs and certain auto-antibodies (antimitochondrial antibody type B, anti LKM2, anti CYP1A2, anti CYP2E1) (although tests for these antibodies may not be available in most local laboratories). Liver biopsy findings of microvesicular steatosis, eosinophilia, centrilobular necrosis, mixed lesions and bile duct injury are all in keeping with drug-induced injury.

Difficulties arise because hepatotoxicity may be asymptomatic for a considerable time before presentation and there may be unknown previous chronic liver disease. Patients are often taking multiple drugs and frequently take additional, sometimes undisclosed, substances such as herbal remedies, over the counter products or cures sold over the Internet, as well as drugs of abuse.

Treatment, in the main, consists of early recognition and prompt withdrawal of the offending agent. A few specific antidotes exist (N-acetyl cysteine for paracetamol, carnitine for sodium valproate) but in the vast majority of cases treatment is simply supportive. Recognition of adverse prognostic signs (such as rising prothrombin time, creatinine or bilirubin, and worsening acidosis, particularly in those at the extremes of the age range) with

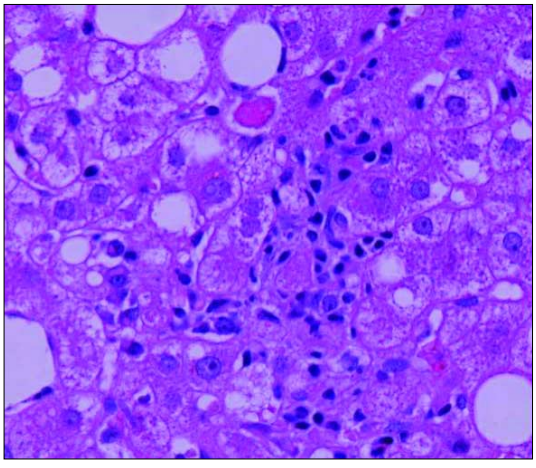


Figure 5. A fatty liver hepatitis in patient with breast cancer taking tamoxifen.

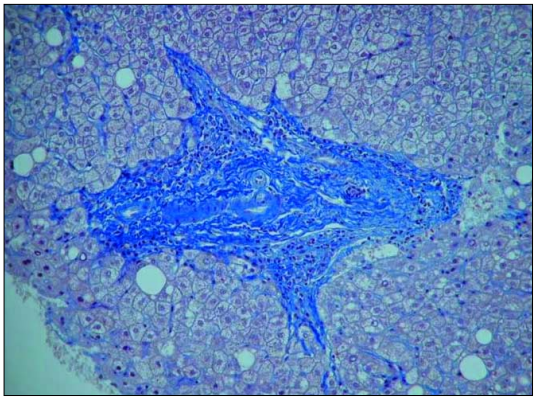


Figure 6. Liver biopsy from a patient with psoriasis who had been taking methotrexate for 3 years. It shows an expanded portal tract with fibrous spurs. Mild large droplet fatty change is also present.

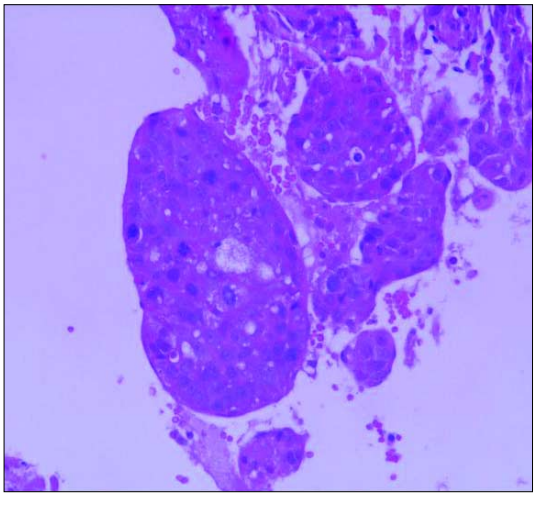


Figure 7. A liver cell cancer in a patient who had received long-term androgenic steroids for Fanconi's anaemia.

prompt referral to a transplant centre can be life saving.

SOME COMMON HEPATOTOXIC DRUG REACTIONS

Even very 'safe' drugs can cause liver damage in certain individuals. If the drug is very widely prescribed then these adverse effects will be seen more commonly. This section will explore some of the clinical patterns seen with common drugs, although only a tiny minority of drugs can be discussed in any detail.

Drugs for diabetes and lipid lowering

Diabetes, hyperlipidaemia and hypercholesterolaemia can all lead to hepatic steatosis, which can cause hepatic damage in its own right. This should be borne in mind when observing abnormal liver biochemistry in individuals taking drugs to treat these conditions.

Statins: Elevation of the transaminases is seen in approximately 3% of individuals taking these drugs. This is probably a class effect, is dose dependent and usually occurs in the first 3 months of therapy. A mixed cholestatic picture that often settles is the norm. In contrast with rhabdomyolysis, abnormal liver blood tests are not more common in people taking fibrates in addition to the statin.

Sulphonylureas: A cholestatic or granulomatous hepatitis may be seen with these drugs, sometimes with a vanishing bile duct-type syndrome. Hypersensitivity features may also be present.

Thiazolidinediones: The most notorious of these agents, troglitazone, was withdrawn in the post-marketing phase after several cases of cholestatic hepatitis with submassive necrosis lead to death or liver transplant. Symptoms were often delayed. The damage probably resulted from a metabolite generated by CYP3A4 and 2CA (He et al, 2001). The other thiazolidinediones appear to be safe and are in clinical use.

Antipsychotics

Cholestasis is common in association with treatment with chlorpromazine, haloperidol, prochlorperazine and sulpiride. Prognosis for recovery is good and usually speedy. Vanishing bile duct syndrome has been reported. In contrast, clozapine and the newer agent risperidone cause a mainly hepatocellular injury.

Anticonvulsants

As enzyme inducers, phenytoin and carbamazepine frequently cause trivial elevations in gamma glutaryl transaminase levels, which can be responsible for a surprising number of outpatient consultations. A more severe syndrome seen with these two drugs and also the more recently introduced lamotrigine is the reactive metabolite syndrome (also known as pseudomononucleosis), which classically occurs after 1–8 weeks of exposure with fever, rash, lymphadenopathy and internal organ involvement, often manifesting as the Stevens–Johnson syndrome. Up to 50% of cases involve the liver and produce acute hepatocellular injury. This syndrome occurs in $10–100/10^5$ treated cases and although the exact mechanism is unknown, an immune basis seems likely.

Microvesicular steatosis with sodium valproate is a rare but life-threatening form of hepatotoxicity, which is more common in children under 3 years of age and those with mitochondrial defects. Replacement of carnitine in these cases is life saving.

Amiodarone

Up to 80% of people taking amiodarone long term (over 1 year) will develop abnormal liver biochemistry, although clinically significant liver disease occurs in the minority. The blood picture is one of hepatocellular injury and histologically the lesion is a steatohepatitis, commonly resembling alcoholic hepatitis. Liver biochemistry usually resolves a month or so after stopping. However, damage may be insidious and lead to cirrhosis.

Antimicrobials

Beta-lactams: Flucloxacillin causes a cholestatic hepatitis about 1 in 10^5 treated cases. Risk factors are age >55 years, and treatment for 14 days or longer (Fairley et al, 1993). The biochemical abnormalities usually develop 2–3 weeks after treatment and may persist for months. Occasionally prolonged cholestasis may develop. Amoxycillin rarely causes problems unless combined with clavulanic acid. Liver biochemistry normally resolves within 2 months. Features of hypersensitivity are common.

Macrolides: Erythromycin causes cholestasis, often with pruritis and jaundice (*Figure 4*). Biopsy shows cholestasis and an eosinophilic infiltrate. There is often a rash and peripheral blood eosinophilia to match.

Drugs used to treat tuberculosis: Significant enzyme elevations are seen in about 20% of patients taking antituberculous therapy. Most resolve spontaneously despite continuation on treatment. Multidrug therapy complicates diagnosis and other risk factors such as underlying liver disease are common.

Rifampicin induces cytochrome p450 enzymes that can enhance the production of toxic metabolites. On its own it seldom causes liver problems, but its frequent coprescription with isoniazid enhances toxicity. Isoniazid causes serious hepatotoxicity in about 1% of those taking it. The blood biochemical pattern is hepatocellular and often resembles acute viral hepatitis in its magnitude which may be severe and fatal. Biopsy shows focal hepatocellular necrosis, with lobular and portal tract damage. Resolution is usual on cessation of therapy. Pyrazinamide causes dose-related hepatotoxicity, which is more common and more severe when used together with the other agents. In terms of blame, pyrazinamide is more likely to be the culprit if the toxicity develops after a month of therapy.

Baseline liver biochemistry is mandatory before commencing antituberculous therapy, with investigation of abnormalities before starting treatment if at all possible. If abnormal at baseline, tests should be repeated at 2–4-weekly intervals to check for toxicity. Therapy can be continued in the face of minimally elevated liver enzymes, but should be suspended if the transaminases rise above five times the upper limit of normal until they have returned to baseline.

HERBAL HEPATOTOXICITY

Many of the drugs in widespread use today are derived from natural botanical sources. Many highly toxic substances exist in nature. Unfortunately there is a widespread public misconception that herbal medicines are automatically safe because they are natural and not pharmaceuticals. Unfortunately herbs are drugs just like any other and their increasing use is leading to an increase in observed hepatotoxicity. There are several excellent reviews detailing the spectrum of herbal liver diseases (Stedman, 2002; Fogdin and Neuberger, 2003) and for individual substances there is a useful website (toxnet: http://toxnet.nlm.nih.gov/). Questions about ingestion of these substances should be part of routine history taking.

CONCLUSIONS

Drug-induced liver disease is common and frequently observed in everyday clinical practice. Most reactions are minor abnormalities in liver biochemistry of no clinical relevance. Severe reactions are mainly idiosyncratic and unpredictable, although some patients fall into higher risk groups who should be closely monitored. Diagnosis is largely circumstantial although clinical and chronological data can be applied to identify the cause. This is followed by stopping the drug if serious effects on the liver are developing, with early recourse to referral for liver transplant if needed. Most hepatotoxic reactions will not have been detected in pre-marketing trials and therefore it is vital that reactions are promptly reported to the Medicines Control Agency. HM

Conflict of interest: none.

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KEY POINTS

- Drug-induced liver disease is common.
- Most drug reactions are idiosyncratic.
- Most can be treated by removing the offending drug, but sometimes liver failure may develop.
- The full spectrum of histopathological abnormalities may occur as a result of treatment with drugs.
- A high index of suspicion is required and pharmacovigilance is mandatory.
- Diagnosis is often circumstantial.