DRUG-INDUCED LIVER DISEASE

The liver plays a central role in metabolism in the human body by regulating an array of chemical substances that reach it via the portal vein and hepatic artery.

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Dr Van der Merwe heads the GI-Hepatology research laboratory at the University of Pretoria. He is actively involved in basic research, student support at master's and PhD levels, fellow training, and patient care. He has been awarded fellowships in gastroenterology by the South African Gastroenterology Society on three occasions and has recently been chosen as joint winner of the International Emerging Leaders Program in Sweden.

Chemicals may enter the body as therapeutic drugs or from the environment. Some may be toxic to the liver whereas others only cause damage when converted into toxic metabolites. This article deals only with drug-induced liver damage, although environmental and traditional herbal medicines as well as the widely available alternative medicines as a cause of damage should always be considered in the differential.[1,2]

EPIDEMIOLOGY

Chemical drug-induced hepatotoxicity caused by drugs is a common problem. Most cases of mild injury will not be noticed.[3] Hepatic injury accounted for 6% of adverse drug reactions and more than 14% of lethal adverse drug events in Denmark,[4] while the Acute Liver Failure Study Group in the US found a rate of 52%. This figure was even higher in the UK at 60 - 70%, because paracetamol is widely used in suicide attempts.[4]

MECHANISMS OF INJURY

Some drugs that injure the liver do so in a predictable, dose-dependent manner. Others will only injure the liver in a few individuals, so-called *idiosyncratic* or *allergic* injury. Predictable toxicity is often associated with a characteristic histological appearance, affecting a particular zone of the liver lobule. Idiosyncratic liver toxicity is presumed to be immunogenic, because signs of hepatic injury frequently co-occur with features of an enhanced immune response such as fever, skin rash and eosinophilia. Idiosyncratic drug injury may cause patchy/focal, bridging or panacinar necrosis. Table I lists the injury patterns caused by drugs.

DIAGNOSIS OF CHEMICAL-INDUCED LIVER INJURY

Drug-induced liver disease may present as deranged liver functions detected on routine biochemistry, but may also present as more important liver disease with bleeding tendency, jaundice and confusion due to encephalopathy. Drugs may also worsen pre-existing chronic liver disease and may occur in hospital patients who present with multi-organ failure, making a correct diagnosis very difficult. A high index of suspicion is required when evaluating any patient with deranged liver functions. In some instances drug toxicity should be actively sought by routine screening of patients, for example patients using methotrexate.

The following initial steps should be considered when evaluating deranged liver enzymes:

- Can a causal relationship be established between the use of a drug and abnormal liver functions? For this a detailed drug history should be obtained.

Table I. **Liver injury patterns resulting from drugs**[4]

Category	Examples
Altered liver tests without histological liver disease	
Microsomal enzyme induction	Phenytoin, warfarin, phenobarbital
Hyperbilirubinaemia	Rifampin, novobiocin, flavaspidic acid
Acute hepatocellular injury	
Zonal	
Zone 1	Phosphorus, ferrous sulphate, allyl formate
Zone 2	Beryllium
Zone 3	Paracetamol, carbon tetrachloride, mushroom poisoning, halothane
Non-zonal	
Massive necrosis	Halothane, valproic acid, non-steroidal anti-inflammatory drugs
Bridging necrosis	Isoniazid, alpha-methyldopa
Focal necrosis	Cloxacillin, isoniazid, halothane
Chronic parenchymal injury	
Chronic active hepatitis	Alpha-methyldopa, nitrofurantoin, dantrolene, minocycline
Fibrosis and cirrhosis	Methotrexate, hypervitaminosis A
Fatty liver	
Microvesicular	Tetracycline, valproic acid, didanosine
Macrovesicular	Alcohol, methotrexate, corticosteroids, asparaginase
Phospholipidosis/pseudoalcoholic	Amiodarone, perheziline maleate, sulfamethoxazole-trimethoprim
Granulomatous reactions	Hydralazine, allopurinol, carbamazepine, phenylbutazone, dapsone
Acute cholestasis	
With hepatitis	Chlorpromazine, amoxicillin-clavulanate, erythromycin estolate, piroxicam
Without hepatitis/ductal injury	Oral contraceptive steroids, anabolic steroids
Chronic cholestasis	
Sclerosing cholangitis	Intra-arterial floxuridine, formalin treatment of hydatid cysts
Vanishing bile ducts	Chlorpromazine, flucloxacillin, prochlorperazine, ajmaline, amitriptyline
Vascular lesions	
Hepatic vein thrombosis	Oral contraceptive steroids, total parenteral nutrition
Veno-occlusive disease	Pyrrolizidine alkaloids, oncotherapy, azathioprine
Portal vein thrombosis	Oral contraceptive steroids
Non-cirrhotic portal hypertension	Vinyl chloride, hypervitaminosis A, azathioprine
Peliosis hepatic	Anabolic steroids, oral contraceptive steroids, thorotrast
Nodular regenerative hyperplasia	Azathioprine, 6-thioguanine
Sinusoidal dilation	Oral contraceptive steroids
Prolapse of hepatocytes into the central veins	Anabolic steroids
Hepatoportal sclerosis	Arsenic azathioprine
Hepatic tumours	
Adenomas	Oral contraceptive steroids, anabolic steroids
Nodular transformation	Oral contraceptive steroids, anabolic steroids, aniline-rapeseed oil, oncotherapy
Hepatocellular carcinoma	Oral contraceptive steroids, anabolic steroids, thorotrast
Angiosarcoma	Inorganic arsenic, thorotrast, vinyl chloride
Cholangiocarcinoma	Thorotrast
Pigment deposition	
Lipofuscin	Phenothiazine, phenacetin, aminopyrine, cascara
Haemosiderin	Alcoholism, iron overload syndromes, toxic porphyries
Gold	Gold compounds used in the treatment of arthritis
Titanium	Drug abuse, occupational exposure

Chemical drug-induced hepatotoxicity caused by drugs is a common problem.

Some drugs that injure the liver do so in a predictable, dose-dependent manner. Others will only injure the liver in a few individuals, so-called idiosyncratic or allergic injury.

- Is underlying liver disease present? Patients with underlying liver disease may have more severe drug reactions, e.g. patients with alcoholic liver disease or fatty liver disease may decompensate when using 'therapeutic' doses of paracetamol or NSAIDs.
- How sick is the patient? Deranged liver functions in an otherwise healthy patient are managed very differently from those in an acutely ill patient with jaundice and encephalopathy. Does the patient need to be admitted or referred to a specialised unit?
- Can the pattern of enzyme abnormalities help predict the mode of injury and the most likely offending drug? Hepatocellular injury is indicated if the ALT is 2 × normal whereas cholestatic injury should be suspected with the ALP 2 × normal. Very often mixed patterns are present.[5]
- When is a liver biopsy indicated? In the author's opinion a liver biopsy is rarely justified or needed when liver enzymes are mildly elevated (< 2 - 10 × normal), if the drug is known for hepatotoxicity, and if there is a prompt response to stopping the drug, that is a reduction > 50% of the excess above the upper limit of normal within 8 days in the case of hepatocellular injury.

TREATMENT

Drug-induced hepatitis is treated by stopping the offending drug. However, there are instances where it is safe, in the absence of other liver diseases, to simply monitor mildly elevated liver enzymes without stopping the drug.

DRUGS THAT COMMONLY CAUSE DRUG-INDUCED HEPATITIS IN CLINICAL PRACTICE

Many drugs have been described that can cause drug-induced hepatitis. However, in clinical practice in South Africa the most common drugs that are seen to cause drug-induced hepatitis are NSAIDs, antibiotics and methotrexate.

Non-steroidal anti-inflammatory drugs

- NSAIDs, as a group, are an important cause of drug-induced hepatitis. The overall incidence of important liver dysfunction is only 0.1%. But because so many people use NSAIDs regularly, hepatotoxicity is commonly seen.
- Hepatotoxicity has been described for all NSAIDs.
- Risk factors for developing hepatotoxicity from NSAIDs include advanced age, renal insufficiency, high doses and concomitant drug use.
- Hepatotoxicity appears to be due mainly to idiosyncratic drug reactions.
- Histologically, NSAIDs cause patchy to massive hepatocellular necrosis along with features such as granulomas, eosinophilia, cholestasis and sometimes even changes of chronic hepatitis.

Antibiotics

Amoxicillin-clavulanic acid (Augmentin)

- Many case studies have been described, and the incidence is 1:80 000 - 1:100 000.
- Risk factors include male sex, advanced age and prolonged treatment.
- Hepatotoxicity appears to be immunological hypersensitivity.
- Jaundice with pruritus commonly develops. Biochemically bilirubin and ALP are elevated. Aminotransferases may be elevated 2-10-fold.
- Histologically cholestasis is seen with perivenular bile stasis, focal injury to interlobular bile ducts and, rarely, granulomas.
- Complete recovery occurs in most cases if the drug is stopped. In the elderly resolution may be prolonged and may take up to a year. Fatal outcomes have been described.

Nitrofurantoin (Macrodantin)

- Nitrofurantoin, a drug commonly used to prevent recurring urinary tract infections, is known to cause chronic liver disease.
- The chronic hepatitis caused by nitrofurantoin commonly occurs when the drug is taken for more than 6 months, and the condition simulates autoimmune hepatitis. Antinuclear and anti-smooth-muscle antibodies are frequently found.
- A rarer acute hypersensitivity reaction manifesting within the first weeks of therapy has also been described.
- Biochemically, elevations are seen in transaminase levels in patients taking the drug for more than 6 months. In the acute form, cholestatic injury may be evident. Cirrhosis may develop and lung involvement with pulmonary fibrosis may co-occur with the liver disease.
- Histological features may simulate autoimmune hepatitis and cirrhosis may be seen with longstanding exposure. In the form that presents acutely, hypersensitivity changes may be seen including cholestasis.
- Withdrawal of the drug is essential and corticosteroids are not helpful. Case fatalities due to end-stage liver disease have been described.

Anti-rheumatic drugs

Methotrexate

- Methotrexate is commonly used in the treatment of rheumatoid arthritis, psoriasis, inflammatory bowel disease (Crohn's disease) and leukaemia. Good understanding of the side-effects is essential.
- Hepatotoxicity is common, although

the exact mechanism of liver injury remains unknown.
- Risk factors for hepatotoxicity include pre-existing liver disease, alcohol use, prolonged use and cumulative dosing exceeding 1.5 g as well as obesity and diabetes mellitus (both associated with underlying steatosis).
- Liver function abnormalities may not reflect the underlying liver injury and patients with near-normal enzymes may have extensive fibrosis.
- Prevention of hepatotoxicity should include avoidance of methotrexate therapy in patients with underlying liver disease or a history of alcohol abuse and will also require close monitoring. Liver biopsies are still advocated when cumulative doses of 1.5 g are reached.
- Moderate to severe fibrosis or cirrhosis requires withdrawal of methotrexate therapy.

Hypolipidaemic agents

3-Hydroxy-3methylglutaryl-CoA reductase inhibitors

- Drugs in this class include simvastatin, atorvastatin and pravastatin.
- Minor elevations in transaminases are common and are not of any consequence.
- More serious liver injury has been described.
- Liver injury is presumed to be mediated by idiosyncratic immune mechanisms.
- Cholestatic or mixed liver injury patterns are normally observed biochemically.
- Recently, investigators reported that hepatotoxicity was not more common in patients with deranged liver functions than in controls.[6]

Owing to space constraints, case studies could not be included in this article. However, the author will be happy to provide these on request (e-mail: **sudm@doctors.netcare.co.za**).

References available on request.

IN A NUTSHELL

Drug-induced liver disease is common in clinical practice, accounting for between 6% and 70% of adverse and lethal drug reactions.

Some drugs that injure the liver do so in a predictable, dose-dependent manner.

Other drug-induced liver injury is peculiar to the individual and is called idiosyncratic or allergic.

Drug-induced liver disease may be an incidental finding on routine monitoring of liver function, or may present as frank liver disease.

Evaluation of drug-induced liver disease requires that the following questions be asked:
- Can a causal relationship be established between the use of a drug and abnormal liver functions?
- Is underlying liver disease present?
- How sick is the patient?
- Can the pattern of enzyme abnormalities help predict the mode of injury and the most likely offending drug?
- When is a liver biopsy indicated?

Drug-induced liver disease is usually treated by stopping the drug.

In some cases, where no other liver disease is present and the enzyme derangement is mild, liver function can simply be monitored without stopping the drug.

Drugs that are most commonly implicated in drug-induced liver disease in South Africa are NSAIDs, certain antibiotics and methotrexate.