Canterbury District Health Board
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Clinical Pharmacology Bulletin

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Drug-induced liver injury (DILI)

Background
More than 900 drugs, toxins, and herbs have been reported to cause liver injury, and drugs account for 20-40% of all instances of fulminant hepatic failure. The most common non-drug causes of liver injury include viral hepatitis, and biliary obstruction.

Drug-induced liver injury (DILI) may not emerge from clinical trial data, as the trials are usually limited in numbers. However, after a drug has been approved, large numbers of patients are exposed, and rare toxic effects, such as DILI, may emerge. DILI is the most common reason cited for withdrawal of approved drugs. The manifestations are highly variable, ranging from asymptomatic elevation of liver enzymes to fulminant hepatic failure.

Risk factors
- Ethnicity – some ethnicities may be more susceptible to toxicity e.g. Afro-Caribbean and Hispanics with isoniazid
- Age – elderly are at increased risk due to decreased clearance, polypharmacy, drug interactions, reduced hepatic blood flow and lower hepatic volume
- Gender – more common in females
- Alcoholism
- Chronic liver disease – patients with pre-existing liver disease may be more susceptible, but this is variable
- Genetic factors – genetic differences in the P450 enzymes can result in increased concentrations of some hepatotoxic drugs. Idiosyncratic reactions can also occur
- Other comorbidities – e.g. AIDS, malnutrition
- Drug formulation – long-acting drugs may cause more injury than shorter-acting drugs

Patterns of DILI
Predictable – more common, occurs within a few days and is dose-related, such as with paracetamol overdose
Unpredictable (idiosyncratic) - uncommon, occur in 1 week to 1 year, and may or may not be dose related. An example is amoxicillin/clavulanic acid. It is therefore important, to take a good drug history and include medications that have been taken over the preceding months.

Remember to ask about herbals and medications purchased at the pharmacy or supermarket. See table below for examples of drugs that can cause various patterns of liver injury.

The principal patterns of liver test abnormalities are:

Hepatitis (hepatocellular) - characterised by a predominant rise in the concentration of transaminases and results from either apoptosis or necrosis of hepatocytes. The current classification is alkaline aminotransferase (ALT) ≥3 times upper limit of normal (xULN) and an ALT/alkaline phosphatase (ALP) ratio ≥ 5. This pattern is more commonly accompanied by acute liver failure.

Cholestasis - characterised by a predominant rise in serum ALP concentration and is usually due to injury to the bile ductular cells either directly by the drug or its metabolite, or indirectly by an adaptive immune response. The current classification is ALP ≥2 xULN and an ALT/ALP ratio ≤ 2.

Mixed hepatitis/cholestasis - characterised by a combination of acute hepatitis and cholestasis. The current classification is ALT ≥3 xULN, ALP ≥2 xULN and an ALT/ALP ratio >2 to <5.

Monitoring
Patients should be asked to report non-specific symptoms that develop after the introduction of a drug (such as nausea, anorexia, malaise, fatigue, right upper quadrant pain, or pruritus), which may indicate hepatotoxicity. Early recognition is essential. Monitoring hepatic enzyme concentrations is appropriate and necessary with a number of drugs, especially with those that can lead to overt liver injury, such as leflunomide, methotrexate and valproate. For drugs that produce liver injury unpredictably, biochemical monitoring may be less useful.

Treatment
The first step is to discontinue the suspected drug. Treatment is largely supportive and based on symptomatology. Other than the use of N-acetylcysteine for paracetamol induced hepatotoxicity, there are no specific antidotes for DILI.

Table: Examples of hepatitis and cholestasis/mixed patterns of drug-induced liver injury

Pattern of liver injury	Type	Examples
Hepatitis	Immune-mediated[1]	Allopurinol, diclofenac[2], halothane, methyldopa, minocycline, **nevirapine**, nitrofurantoin, phenytoin, propylthiouracil.
	Non-immune-mediated[3]	Acarbose, amiodarone, bosentan, dantrolene, diclofenac[2], disulfiram, flutamide, HAART[5] therapy, HMG-CoA reductase inhibitors ('statins'), **isoniazid**, ketoconazole, labetalol, **leflunomide**, **methotrexate**, **nevirapine**, nicotinic acid, **paracetamol**, pyrazinamide, rifampicin, tolcapone, **valproate**.
Cholestasis/mixed	Immune-mediated[1]	ACE inhibitors, **amoxicillin/clavulanic acid**, carbamazepine, chlorpromazine, cotrimoxazole (trimethoprim/sulfamethoxazole), erythromycin, phenobarbital, sulphonamides, sulindac, tricyclic antidepressants.
	Non-immune-mediated[3]	Anabolic steroids, azathioprine, **ciclosporin**, oestrogens, oral contraceptives, terbinafine.

[1] Immune-mediated: may be characterised by fever, rash, eosinophilia or autoantibodies; rapid positive re-challenge occurs in some.
[2] Reaction to diclofenac may be either immune-mediated or non-immune mediated.
[3] Non-immune mediated: not characterised by fever, rash, eosinophilia or autoantibodies.
[4] HAART = highly active antiretroviral therapy.
Bold drugs - DILI is reported more frequently