

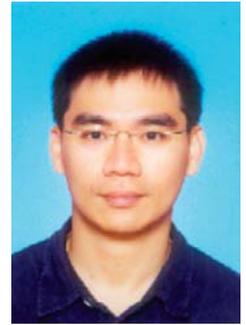


Drug-induced Liver Injury: An Update

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Introduction

The liver is a major organ for metabolism of foreign substances and also functionally interposed between the site of resorption and the systemic circulation. These conditions render the liver not only the most important organ for detoxification of foreign substances but also a major target of their toxicity. More than 1000 drugs have been associated with idiosyncratic hepatotoxicity and drug-induced liver injury (DILI) is the main reason for removing approved medications from the market. Moreover, drug-induced hepatotoxicity contributes to more than half of the cases of acute liver failure, with paracetamol being the principal offending agent in western countries. In Sweden, hepatic injury due to drugs occurred in 2.3% of patients hospitalised for jaundice¹. However, the real incidence of DILI remains unknown because of the difficulty in establishing diagnosis and the low reporting frequency to the pharmacovigilance authorities². DILI represents a clinical challenge due to the large number of reported hepatotoxic drugs in current use, the broad spectrum of hepatic injuries by which it may manifest and the frequent absence of clinical findings that permit its diagnosis with certainty. Delay in the diagnosis of DILI may result in unnecessary extensive investigations and poor patient outcomes including acute liver failure and cirrhosis. The purpose of this review is to discuss the causality assessment of DILI in clinical practice and update the recent advances in the understanding of hepatotoxicity of some commonly used drugs and herbs, especially among patients with underlying liver disease.

Patterns of drug-induced liver injury

Hepatotoxicity may be predictable or unpredictable. Predictable reactions typically are dose-related and occur with short latency (within a few days) after some threshold for toxicity is reached. Paracetamol (acetaminophen) is a classic example. Conversely, idiosyncratic reactions occur with variable, sometimes prolonged latency (1 week to 1 year), with low incidence and, may be or may not be dose-related. On the basis of the alanine aminotransferase (ALT) and alkaline phosphatase (ALP) levels, the liver test abnormalities are classified into hepatocellular, cholestatic, and mixed patterns. Hepatocellular injury is characterised by the marked elevation of ALT level, usually preceding increase in total bilirubin level and modest increase in ALP level. The elevation of ALT level tends to resolve over the course of several weeks after discontinuation of the offending agent. Sometimes asymptomatic liver test

abnormalities resolve despite continued drug use, a phenomenon referred to as adaptation.

Cholestatic injury involves a predominantly increase in ALP level as a result of canalicular cholestasis or ductular injury. It is usually not as life-threatening as hepatocellular injury, but it may lead to chronic ductopenia and rarely cirrhosis. In a mixed pattern of DILI, patients present with a combination of acute hepatitis and cholestasis. Of the three patterns of liver injury, hepatitis is more commonly accompanied by acute liver failure. In a Spanish registry, more than 10% of patients with drug-induced hepatocellular injury and jaundice may progress to death or requiring liver transplantation. The combination of coagulopathy and encephalopathy occurring within 26 weeks after the onset of illness in a patient without pre-existing cirrhosis carries a poor prognosis in the absence of liver transplantation.

Causality assessment of DILI

The presentation of DILI ranges from asymptomatic elevation of ALT level to acute liver failure and may mimic all forms of acute and chronic liver disease. High index of suspicion is paramount especially in patients using prescription or nonprescription medication or even dietary supplements. Other causes of liver disease must be ruled out. In appropriate clinical settings, sepsis-induced cholestasis and liver injury due to heart failure or "shock liver" should be considered. The hepatic dysfunction due to some non-drug causes is summarised in Table 1.

The Roussel Uclaf Causality Assessment Method (RUCAM) is the most widely-used methods for assessing non-organ-specific drug reaction to well-defined hepatic reactions³. The RUCAM is based on 7 major criteria, namely (1) time to onset, (2) course of the reaction, (3) risk factors for the reaction, (4) assessing the role of concomitant therapies, (5) screening for non-drug-related causes, (6) weighing the information known about the DILI in question, and (7) confirmation of the reaction by positive rechallenge or in vitro assays. A causal relationship is graded as: excluded, unlikely, possible, probable, and highly probable. Liver biopsy is not considered as a diagnostic criterion for DILI as most of the histological changes may be non-specific and provide only circumstantial evidence that a drug is involved. Therefore biopsy is reserved for patients who have acute injury that fails to resolve or alternative diagnosis is suspected.

Table 1 Common non-drug causes of liver impairment

Aetiologies	Diagnostic tests
Viral hepatitis	
Hepatitis A virus	HAV Ig M
Hepatitis B virus	HBc IgM and HBs Ag
Hepatitis C virus	Anti-HCV antibodies, HCV RNA
Hepatitis E virus	HEV IgM
Biliary tract diseases	Abdominal ultrasonography, ERCP, MRCP
Alcohol	Gamma glutamyltransferase
Autoimmune diseases	
Autoimmune hepatitis	Type 1: anti-smooth muscle antibodies, anti-nuclear factor Type 2: anti-liver kidney-microsomal antibodies
Primary biliary cirrhosis	Anti-mitochondrial antibodies
Haemodynamic disorders	
Heart failure	Echocardiography
Ischaemia/ hypoxia	Clinical scenario
Budd-Chiari syndrome	Doppler ultrasound
Portal vein thrombosis	Doppler ultrasound
Veno-occlusive disease	Liver biopsy
Metabolic/ genetic diseases	
Wilson's disease	Diminished serum ceruloplasmin, elevated urinary and serum copper
Haemochromatosis	Elevated iron saturation and ferritin levels
Sepsis-induced cholestasis	Sepsis work-up

Table 2. Commonly-reported drugs associated with drug induced liver injury (DILI)

Drugs associated with DILI
Paracetamol
Non-steroidal anti-inflammatory drugs
Diclofenac
Ibuprofen
Naproxen
Antibiotics
Amoxicillin/ clavulanate (augmentin)
Flucloxacillin
Erythromycin
Ciprofloxacin
Anti-tuberculosis drugs (Isoniazid, rifampicin, pyrazinamide)
Anti-retroviral drugs (e.g. ritonavir)
Immunosuppressants
Azathioprine
Cyclophosphamide
Anti-arrhythmia drugs
Amiodarone
Anti-epileptics
Phenytoin
Carbamazepine
Valproic acid
Psychiatric drugs
Chlorpromazine
Paroxetine

Common hepatotoxic agents

Paracetamol

The most commonly implicated drugs involved in acute liver injury and their disease patterns are summarised in Table 2. Paracetamol poisoning is the leading cause of drug-induced fulminant hepatitis in the United States. Traditionally, it is believed that a minimum of 7.5 - 10g of paracetamol is needed to produce hepatic necrosis in an adult. In the analysis of acute paracetamol-induced hepatotoxicity of the Acute Liver Failure Group in the United States⁴, a median dose of 24g was ingested with 44% of the cases due to an intentional (suicidal) overdose. However, they found one patient who developed liver failure after taking only 1.2g of paracetamol, which is barely above a single therapeutic dose. It is possible that paracetamol (in non-toxic doses) may act as a cofactor with viral hepatitis or other medications to produce acute liver failure - a so-called 'dual pathology' scenario. Indeed, old age, the presence of underlying liver disease, poor nutritional status and the combination use of alcohol and opiates with paracetamol are all risk factors for paracetamol poisoning. Furthermore, long-term (about 1 year) exposure to paracetamol (3-4g daily) can also lead to chronic liver injury.

Interestingly, paracetamol poisoning appears less common among Chinese and it is possibly due to the different habit of drug usage between Chinese and Caucasians. A pharmacokinetics study from our locality⁵ showed that Chinese subjects appeared to be better protected against paracetamol hepatotoxicity by having more rapid absorption of paracetamol, as well as a tendency to produce less toxic metabolites. However, further studies about the possible ethnic differences in paracetamol metabolism are needed before definitive statements can be made.

Augmentin (amoxicillin/ clavulanic acid)

According to various registries and retrospective studies in European countries and the United States, antibiotics (including anti-tuberculosis drugs) are the most common agents causing DILI followed by non-steroidal anti-inflammatory drugs (NSAIDs), with diclofenac most often responsible for the DILI⁶. It is worth mentioning that amoxicillin/clavulanic acid (augmentin) is the most frequently reported antibiotic associated with DILI. The estimated risk of symptomatic hepatitis due to augmentin is <1 in 100,000 persons exposed. Interestingly, age is found to be the most important determinant in the biochemical expression of augmentin-induced hepatotoxicity⁷. Patients younger than 55 years of age exhibit predominantly hepatocellular damage, which occurs at 1 week after exposure to the drug while cholestatic liver injury occurs mostly at 2-3 weeks and the mixed liver injury proportionally predominates after 3 weeks. In a prospective study by Andrade et al. in Spain, they reported that 13% (59/446) of their in- and out-patients suffering from acute DILI were due to augmentin and 6% of them developed acute liver failure or progressed to chronic liver disease and cirrhosis⁸. This brings into the question the generally-held opinion that the clinical outcome of hepatotoxicity caused by augmentin is invariably toward recovery.

Anti-tuberculosis drugs

Approximately 10-20% of patients receiving isoniazid will develop mild to moderate elevation of ALT and about 0.1% develops clinical hepatitis. Slow acetylator status and genetic polymorphism of CYP2E1 have been identified as risk factors. The concomitant intake of rifampicin or pyrazinamide significantly increases the



risk of liver disease to 2-4%, which can be partly explained by an induction of CYP450 enzymes.

There is a continuous interest in hepatitis B as a risk factor for anti-tuberculosis drugs-related hepatotoxicity. In 1990, a Taiwan study⁹ showed that 2.4% of patients treated with isoniazid, rifampicin and ethambutol developed symptomatic hepatitis of which, more than 35% were hepatitis B carriers and about half of them developed liver failure subsequently. In contrast, the mortality rate for non-hepatitis B carriers was less than 4%. Recent studies have shown that about 35-59% of hepatitis B carriers will develop abnormal liver function tests during anti-tuberculosis treatment and 25-50% of them are symptomatic.

Thus, it is recommended that a baseline clinical and laboratory evaluation, including liver function and hepatitis B surface antigen, should be performed before the start of anti-tuberculosis treatment. And patients should be taught to recognise symptoms of hepatitis and to report them promptly. Patients with risk factors for hepatotoxicity for example, those with preexisting liver diseases, the alcoholics, the elderly and malnourished should have their liver function monitored regularly. In fact, a study from India¹⁰ has shown that periodic biochemical monitoring in patients receiving anti-tuberculosis therapy allowed for early detection of hepatotoxicity at an early stage and reintroduction of therapy was successful in nearly all patients after initial recovery. According to the Consensus statement of Department of Health and Hospital Authority in Hong Kong in 2002, anti-tuberculosis treatment should be withheld if ALT > 3x of upper limit of normal (ULN) or bilirubin is greater than 2x ULN and non-hepatotoxic regimen (based on streptomycin, ethambutol and fluoroquinolone) may be reintroduced when ALT level < 2x ULN. Potential hepatotoxic drugs can be reintroduced sequentially once liver function is normal. Whether anti-viral therapy for hepatitis B infection reduces the risk of developing anti-tuberculosis drug-related hepatotoxicity remains uncertain. We have reported a successful case of reintroduction of isoniazid and rifampicin after adding lamivudine in a chronic hepatitis B patient¹¹. Large-scale prospective studies are warranted to address this important clinical question.

Anti-diabetic drugs

Thiazolidinediones

Thiazolidinediones are insulin-sensitising agents used to treat diabetes mellitus through activation of the gamma isoform of the peroxisome proliferators-activated receptor (PPAR γ). Troglitazone, the first approved Thiazolidinediones, was withdrawn from the market in 2000 following 94 reported cases of liver failure. An idiosyncratic mechanism of toxicity was suggested based on the delayed onset of ALT elevation and a lack of dose effect. Rosiglitazone and pioglitazone were introduced into the market by the time troglitazone was withdrawn and both did not show an increased risk of ALT elevation in early clinical trials. Chalasani et al.¹² also showed no difference in the rate of ALT elevation between diabetics with and without

elevated baseline ALT level after taking rosiglitazone, suggesting that diabetics with elevated baseline ALT are not at a higher risk of hepatotoxicity from rosiglitazone. Indeed, a significant proportion of diabetic patients with abnormal liver tests at baseline had a decrease in ALT while taking rosiglitazone, which is probably due to the improvement in underlying fatty liver disease while discontinuing pioglitazone in patients with nonalcoholic steatohepatitis (NASH) may result in subsequent elevation in ALT levels and worsening of liver parenchymal inflammation¹³. On the other hand, case reports of granulomatous hepatitis, cholestatic liver injury and fulminant liver failure due to rosiglitazone or pioglitazone have been reported. It is therefore advisable that thiazolidinediones should not be withheld in diabetics with minor liver dysfunction (ALT < 2.5x ULN) in the setting of NASH, especially given the potential beneficial effects, but it is prudent to monitor liver function tests during therapy.

Statin

Statins, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, are commonly used for hyperlipidaemia and form an important part of a preventative strategy against cardiovascular morbidity and mortality. Asymptomatic mild ALT elevation is a class effect of statins, and it does not indicate liver dysfunction. The incidence of ALT > 3x ULN associated with the use of statins is 0-3% and the rate has shown to be comparable with placebo in several trials. Clinically significant hepatotoxicity caused by statins remains extremely rare. Hepatocellular, cholestatic, and mixed patterns of liver injury have been reported in the literature. So far, there is no evidence to support routine monitoring of liver enzyme levels in patients receiving statins as it may result in high false-positive rates and unnecessary discontinuation of a drug that might be otherwise beneficial.

Although not evidence-based, current recommendations discourage the use of statins in patients with pre-existing liver disease. But this practice is problematic, because hyperlipidaemic patients have a significant prevalence of underlying NASH resulting in an elevated ALT level. Patients who have NASH would benefit from statins because of their heightened risk of cardiovascular disease. Furthermore studies showed that patients with compensated hepatitis C infection or primary biliary cirrhosis were not at higher risk for statin hepatotoxicity. Emerging data, in fact, suggest that statins are actually beneficial in patients who have underlying liver disease¹⁴. Thus, the Liver Expert Panel has made recommendations to the National Lipid Association that the presence of chronic liver disease and Child's A cirrhosis should not be considered as a contraindication for statin use, and that the current evidence supports the use of statins to treat hyperlipidaemia in patients with NASH¹⁵.

Herbal products

Herbal medicine is widely used for the treatment of many common diseases in western countries as well as in Hong Kong. About 10% of adults in Hong Kong have consulted traditional Chinese medicine doctors and



13.5% have been using traditional Chinese medicine drugs. In a local survey¹⁶, 32% of chronic hepatitis B patients have received traditional Chinese medicine. Herbal medicine is usually believed as 'natural', harmless and without side-effects. However a German study¹⁷ showed that 0.9% of patients on Chinese herbal medicine had a more than 2-fold elevation of ALT level. A prospective study from Queen Mary Hospital showed that 7 of 45 (15.6%) chronic hepatitis B patients developed liver dysfunction attributable to traditional Chinese medicine and 3 of them developed liver failure resulting in death or requiring liver transplantation¹⁸. The common Chinese herbal medicines with potential hepatotoxicity are listed in Table 3. Diagnosing herb-induced hepatotoxicity is a major challenge to clinicians and sometimes impossible in some cases. Many patients often do not disclose the use of herbal medicines spontaneously and physicians should make specific inquiries about the use of herbal medicine. Many herbal formulae contain a list of different herbs of different dosages which make us difficult to impute the toxicity to a single herb. The amount of the herbs taken by patients, the possible interactions between different herbs and western medicines, the synergistic hepatotoxicity of herbal preparations, and risk factors of patients have to be considered. Additional problems with formulation of herbal medicines include botanical misidentification, product contamination or adulteration, and mislabelling and variability in the collection and extraction processes.

Table 3. Some common Chinese herbal medicine associated with hepatic dysfunction

Chinese Name	Plant/Component
千里光	Herba Senecionis Scandentis
川棟子	Fructus Toosendan
五倍子	Galla Chinensis
及己	Radix Chloranthi Serrati
天花粉	Radix Trichosanthis
石榴皮	Pericarpium granati
魚膽	Fish gallbladder
黃藥子	Tuber Dioscoreae Bulbiferae
雷公藤	Tripterygium wilfordii Hook
蒼耳子	Fructus Xanthii
喜樹	Fructus seu Radix Camptothecae Acuminatae
蜈蚣粉 (川足)	Dried centipede
石蠶	Germander (Teucrium chamaedrys)
金不換	Lycopodium serratum
麻黃	Ephedra sinica
小柴胡湯 (柴胡, 半夏, 生薑, 黃芩, 大棗, 人參, 甘草)	Xiao-chai-hu-tang (Bupleurum falcatum, Scutellaria baicalensis, etc.)
胡薄荷油	Pennyroyal oil (pulegone)
虎杖	Rhizoma Polygoni Cuspidati

Conclusions

Drug-induced liver diseases mimic various forms of liver injury that range in severity from transient, asymptomatic elevation in ALT levels to fulminant liver failure. The diagnosis of DILI is predicated on the exclusion of other possible causes and on the identification of a clinical signature that consists of the pattern of liver test abnormality, the duration of latency to symptomatic presentation, and the response to drug withdrawal. Administration of drugs in patients with underlying liver disease involves a balanced assessment of risk-benefit ratios that may favour judicious use when clear indications are present, as in the case of statins. Further studies are needed to provide better understanding of the pathogenesis and susceptibility to drug-induced liver injury which may in turn facilitate the prediction of human toxicity and provide better biomarkers for diagnosing DILI.

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