Drug-induced liver injuries

Drug-induced liver injury is a significant cause of liver disease, including chronic liver disease.

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Drug-induced liver injury (DILI) is a term increasingly being used by most clinicians and is synonymous with drug-induced hepatotoxicity. A succinct definition of a DILI is 'a liver injury induced by a drug or herbal medicine resulting in liver test abnormalities or liver dysfunction with a reasonable exclusion of other potential aetiologies'.[1] DILIs are a recognised and clinically significant cause of acute, acute-on-chronic and, less commonly, chronic liver disease. The vast majority are idiosyncratic reactions in contrast to the less common dose-dependent predictable injury to drugs, such as paracetamol in overdose. Drugs remain a significant, if not the leading, cause of acute liver failure in the developed world and a prominent aetiological factor in the developing world. As the true frequency of DILIs in users of most drugs is not known and several epidemiological studies have had major methodological limitations, the true incidence of DILI remains mostly unknown.[1] Nonetheless, DILI is seemingly relatively uncommon, ranging between 1 in 10 000 and 1 in 100 000 drug exposures.[2] Exceedingly few prospective population-based studies have been undertaken to establish the true incidence of DILIs. One such study in France generated an incidence of 13.9 per 100 000, while acute liver injury has been reported to occur in 2 - 10% of patients hospitalised for jaundice; hence the actual population incidence may be higher than is generally appreciated.[3,4] An Achilles heel that often underpins the difficulty in clearly establishing the true incidence of DILIs is demonstrating the causal relationship between a given drug exposure and DILI.[5]

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Elucidating the various mechanisms of drug injuries is beyond the scope of this article; however, several putative mechanisms exist, with drugs or their metabolites behaving as haptens initiating an idiosyncratic immunological response.

An approach to drug-induced liver injuries

Clinical and biochemical signatures of drug injuries

The clinical presentation of a DILI may range from a mildly deranged liver profile to acute liver failure, encephalopathy and jaundice. Although uncommon, cirrhosis may result from a long-standing DILI. The liver enzyme pattern in a patient with a suspected DILI may be the 'signature' pattern for a given drug and can sometimes aid in diagnosis.[1] Hepatocellular patterns, i.e. elevated ALT/AST, are typically seen with drugs such as isoniazid or diclofenac.[2] Cholestatic-type injuries, i.e. elevated ALP/GGT, are seen with amoxicillin/clavulanic acid (Augmentin), macrolide antibiotics or oestrogens, although drug injuries often typically present with a mixed type injury, i.e. a cholestatic hepatitis. Symptoms of a DILI are often highly variable and include nonspecific symptoms, such as fatigue, nausea, abdominal pain, dark urine, jaundice and pruritus. The type of symptoms and pattern of onset may assist in distinguishing hepatocellular injury from cholestatic injury. For example, pruritus typically occurs early in cholestatic injuries but late, if at all, in hepatocellular injury. Symptoms of hypersensitivity, such as fever, rash, lymphadenopathy and eosinophilia, are also pointers towards the cause of the injury and are typical for drugs such as phenytoin, sulphonamides and allopurinol.

Causality assessment, excluding other aetiologies

The diagnosis of a DILI centres on two important aspects – suspicion and exclusion of other common aetiological factors, e.g. viral hepatitis. The timeline between the exposure to a given drug and the onset of symptoms is extremely variable, but typically ranges from a few days to several weeks. Importantly, however, in some instances a lag phase of several months may occur, which emphasises the importance of always maintaining a high index of suspicion and reinforces the critical need for acquiring a careful drug or toxin exposure history.[6] The history should be revisited, repeatedly if necessary, in a non-confrontational manner with patients encouraged to tabulate anything and all they may have used in the weeks before presentation, including all prescribed medications, over-the-counter medications, herbal or health supplements or traditional medicines. As indicated, the crux of a diagnosis of a DILI is the establishment of a causal relationship and key to this 'guilt by association' are several factors, including history of exposure to a given drug, time to onset of symptoms, clinical presentation, exclusion of other possible diagnoses and presence of a 'positive dechallenge', i.e. improvement upon discontinuation of the drug.[5,7] The diagnosis is further strengthened by drug rechallenge, although this should always be very carefully considered.

Liver biopsy

Liver biopsy can be a valuable adjunct in diagnosing a DILI, but while the histological pattern may suggest a drug injury it is not absolutely diagnostic. Furthermore, where a patient is using polypharmacy and has a DILI, it is not possible to ascertain on biopsy which drug is the actual offender. The additional value of a biopsy is to exclude other possible diagnoses, such as autoimmune hepatitis or an unusual drug injury pattern, e.g. nodular regenerative hyperplasia. Some drugs have fairly unique patterns of injury, e.g. amiodarone and steatohepatitis. In cholestatic injuries liver biopsy allows for the evaluation of the severity of the bile duct injury and any features suggesting the development of ductopenia or the 'vanishing bile duct syndrome'. This uncommon yet severe phenomenon on the spectrum of cholestatic drug injuries was first described with flucloxacillin, but has subsequently also been attributed to other drug-induced cholestatic injuries. Limited data exist on the prognostic impact of the histology on the clinical outcome in DILIs. However, in one study the presence of severe hepatic necrosis was associated with a poorer prognosis in halothane or isoniazid-induced liver injury.[8]

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Selected common drug injuries in clinical practice

Paracetamol

Paracetamol is the prime example of a drug that produces a predictable dose-dependent liver injury. It remains the leading cause of acute liver failure in the developed world, with approximately half of cases

being unintentional overdoses, and suicide attempts accounting for the rest. Studies have demonstrated that metabolites for paracetamol are often found in those presenting with cryptogenic acute liver failure. This may suggest causality or even if not directly causal in these cryptogenic patients, it does support the clinical value of the empiric use of *N*-acetylcysteine (NAC) in such patients. Notably the quantum of dose required for toxicity is less in those who chronically use alcohol, as both alcohol and paracetamol share the same cytochrome P450 (*cyp2E1*) metabolising subunit. Paracetamol should always be suspected in those with extremely high ALT/AST and only a mildly elevated bilirubin at presentation. Liver injury typically develops 12 - 72 hours after ingestion, with the onset of liver failure between 72 and 96 hours later.[1] The INR is the best initial predictor of the severity of the injury.

A Swiss study identified 12 cases of severe DILI related to the use of Herbalife, with one patient requiring liver transplantation.

Antituberculosis drugs

The potential hepatotoxicity of first-line TB drugs is well known, as are many of the drugs used in the treatment of MDR/XDR TB. Given the burden of HIV and TB in South Africa, many clinicians have faced the issue of TB drug hepatotoxicity at some point. Rifampicin, isoniazid and pyrazinamide typically produce a hepatocellular-type liver injury days to weeks after initiating TB therapy. Risk factors include concomitant chronic alcohol use and hepatitis B or C infection. As a combination of drugs is used in TB, the precise offending agent is usually not known. An elevation in the transaminases 3 - 5 times above the upper limit of normal or any elevation in a symptomatic or jaundiced patient should prompt the immediate cessation of therapy. After allowing liver enzymes to improve, standard practice is to initiate a stepwise drug rechallenge using appropriate weight-based dosing of the individual drugs. Based on fairly old data pyrazinamide is not reintroduced, although more recent data have suggested that pyrazinamide could be used as part of a drug rechallenge albeit in selected patients and with due caution.[9,10] Any patient with a significant TB DILI presenting with features of liver failure should never undergo drug rechallenge. A common complicating factor in HIV-positive patients is that they may concomitantly be on antiretroviral therapy and co-trimoxazole prophylaxis. The presence of a TB immune reconstitution syndrome involving the liver in patients with HIV/AIDS after initiating ART should not be confused with a DILI. These patients usually develop a hepatomegaly with elevated canalicular enzymes, viz. ALP/GGT, rather than the transaminases, as for a typical TB DILI.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Given their widespread and voluminous (ab)use, NSAIDs are a significant cause of DILI. In a Swedish study diclofenac was the commonest drug implicated as the cause of DILI in an outpatient setting, while in a population-based case-control study diclofenac was the only NSAID associated with an increased risk of clinically relevant DILI (OR 4.1; 95% CI 1.9 - 8.8).[11] Diclofenac, like most NSAIDs, is associated with a predominantly hepatocellular pattern liver injury. In some instances, COX-2 inhibitors such as celecoxib and the less commonly used NSAID sulindac, have been associated with a cholestatic injury.

Antiretroviral therapy (ART)

Hepatoxocity remains a significant adverse effect of all three major classes of ART. In the prospective D:A:D study, liver disease was the major cause of non-AIDS mortality, with ART accounting for 3% of liver-related mortality.[12] Mechanistically, nucleoside reverse transcriptase inhibitors such as didanosine (ddI) and stavudine (d4T) cause lactic acidosis and steatohepatitis by the depletion of mitochondrial DNA through their effect on ϒ-polymerase. This mitochondrial toxicity usually occurs within weeks to months after starting cART and is associated with raised transaminases, serum lactate and lactate dehydrogenase. Long-term liver effects of steatosis are the result of their ability to induce insulin resistance, which may be associated with a lipodystrophy. With non-nucleoside reverse transcriptase inhibitors (NNRTIs), raised liver function tests occur in 1 - 8% of patients using efavirenz and 4 - 18% of those on nevirapine. The risk of nevirapine-induced hepatotoxicity is elevated 12 times in female patients with CD4 counts greater than 250. The mechanism of hepatotoxicity of NNRTIs is thought to be immunoallergic and, as is often the case with nevirapine, may form part of a DRESS syndrome (drug reaction, eosinophilia, systemic symptoms) with accompanying rash.[13] Hepatotoxicity has been observed in 1 - 9% of patients receiving protease inhibitors. The precise mechanism of hepatotoxicity is unclear. It is useful to remember that atazanavir causes an unconjugated hyperbilirubinaemia through an acquired 'Gilbert's syndrome'-like mechanism. This is not regarded as a DILI. Risk factors for the development of hepatotoxicity with cART include hepatitis B or C co-infection, concomitant use of alcohol, abnormal liver function tests at baseline or markers such as low platelets that may suggest unrecognised chronic liver disease and portal hypertension.[13]

Antibiotics

Drugs such as amoxicillin/clavulanate, erythromycin, clarithromycin, flucloxacillin, co-trimoxazole, minocycline and nitrofurantoin are all associated with potential hepatotoxicity. The most common injury pattern is cholestatic, while amoxicillin/clavulanate and flucloxacillin have been associated with causing the 'vanishing bile duct syndrome'. Co-trimoxazole can produce a mixed pattern of injury and, given its widespread use in patients with HIV, should always be considered as a potential cause of abnormal liver function tests in these patients. Minocycline and nitrofurantoin produce a hepatocellular pattern of injury that in some patients develops into autoimmune hepatitis. A useful clinical adjunct is in patients with established chronic liver disease where susceptibility for a DILI may be increased – antibiotic choice should be directed to those with the desired antimicrobial spectrum of activity but known safer hepatotoxicity profiles.

Statins

Asymptomatic elevations in liver enzymes are a well-known adverse effect of all statins. The vast majority of significant statin DILIs are hepatocellular injuries, but cholestatic injuries have also been described. Statins can precipitate autoimmune hepatitis, which is often aggressive and requires long-term immunosuppression. Most package inserts suggest baseline testing of patients about to start a statin; however, this practice has been called into question as some patients' baseline abnormal LFTs actually improve on a statin.[14] These are probably patients in whom abnormal LFTs are caused by non-alcoholic fatty liver disease. While routine

LFT testing may not be necessary in all patients, statins should still be used with caution in patients with underlying chronic liver disease and appropriate monitoring performed. More importantly, cirrhosis is not a contraindication to the use of statins, but due caution should be exercised.

Prompt cessation of the drug(s) implicated is the cornerstone of management in any patient presenting with a suspected DILI.

Herbal and dietary supplements

Herbal preparations and supplements use is a multi-billion dollar global industry. In a prospective study from the DILI network multicentre group in the USA, herbal and dietary supplements were implicated in 9% of DILI cases.[1] In 60% of cases the use of dietary or herbal supplements was intended for muscle building or weight loss. Similarly, a Japanese study revealed that 10% of cases over a 10-year period were attributable to dietary supplements and 7% to Chinese herbal drugs. A Swiss study identified 12 cases of severe DILI related to the use of Herbalife, with one patient requiring liver transplantation.[15] In South Africa an additional factor to consider is that a number of people make use of traditional practitioners. Clinicians should note that in any patient with a DILI these preparations need to be specifically asked about when taking the history, as patients often do not think of these preparations as 'drugs' and equate herbal with natural and being innocuous.

Management of DILIs

Prompt cessation of the drug(s) implicated is the cornerstone of management in any patient presenting with a suspected DILI.

Initially, symptoms are often nonspecific before the onset of overt features; hence any patient who recently initiated a new therapy and complains of vague symptoms should be advised to immediately discontinue the drug, pending confirmation of a possible DILI. Concomitant with confirming a DILI is the simultaneous assessment of the severity of the liver injury. A decision regarding the need and risk of a liver biopsy should be made early because, if the patient should deteriorate, the opportunity to safely do a biopsy may be lost. Symptomatic patients and in particular those who are jaundiced should be hospitalised. Patients with coagulopathy and/or encephalopathy should preferably be admitted to an ICU for intensified acute liver failure management. Patients with suspected paracetamol DILI must receive NAC, with a recent study suggesting some benefit of NAC – also in non-paracetamol-related acute liver failure. In patients with a significant paracetamol injury, i.e. ALT/AST >5 times the upper limit of normal (ULN) or any evidence of liver failure, NAC should be continued beyond the typical schedule at 100 mg/kg/24 h until the INR has normalised and transaminases are ≤5 times the ULN and they are stable off NAC. Corticosteroids are used in those with drug-induced autoimmune hepatitis or where a hypersensitivity syndrome is suspected (e.g. phenytoin). Ursodeoxycholic acid has demonstrated some benefit in small studies for cholestatic drug injuries. For the most part the management of DILI should be supportive, with appropriate bed rest, close monitoring and follow-up.

IN A NUTSHELL

- Drug-induced liver injuries are probably more common than realised, although clinically apparent injuries are less frequent.
- Key to the diagnosis is excluding other common causes of liver disease and establishing a causal relationship between exposure to a drug(s) and a liver injury.
- A careful drug or toxin history is of the utmost importance and should be repeatedly revisited if necessary.
- The pattern of injury, viz. hepatocellular or cholestatic, could be the identifying 'signature' of the injurious drug.
- Liver biopsy is a useful adjunct to the diagnosis and should be considered early in a suspected DILI.
- TB drugs typically produce a hepatocellular-type injury – rechallenge is generally safe unless the drug injury produced any evidence of liver failure.
- All classes of ART are potentially hepatotoxic and should be an adverse effect that clinicians consider in patients on ART who complain of unexplained nonspecific symptoms.
- Herbal/traditional medicines or health supplements must be considered as a cause of a DILI.
- Immediate cessation of the drug(s) is the cornerstone of the management of a DILI.
- In a significant paracetamol injury, NAC should be continued beyond the typical treatment schedule.

SINGLE SUTURE

If it makes you ill, don't get bitter

Can't stand the bitter taste of gin and tonic? Blame it on your ancestors. One of the first studies of the link between strong tastes and nausea confirms that only bitter tastes – not sweet, salty or umami tastes – commonly induce nausea.

The queasiness might be an adaptation to alert us to the presence of toxins, which are often bitter, says Paul Breslin at the Monell Center in Philadelphia, Pennsylvania.

His team asked 63 volunteers to taste intensely bitter sucrose octa-acetate. Afterwards, 65% of them felt nauseous. But none felt queasy after tasting an intensely sweet solution and just one-third felt nauseous after tasting a strong salty or umami solution.

Why 35% of people did not feel nauseous after the bitter taste is unclear, but may show there is no accounting for taste.

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