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Review Article

Drug-Induced Liver Injury (DILI): A Short Review on Current Scenario

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ABSTRACT

Drug Induced Liver Injury (DILI) is acute and chronic liver injury secondary to drugs and herbal compounds. DILI can be caused by overdose or even at therapeutic doses of some drugs such as NSAIDs and antitubercular drugs. It can be direct, indirect or idiosyncratic based on the mechanism of liver injury caused by the drug. It is also classified based on the histopathological and clinical features. Several mechanisms and hypotheses like immune mediation, mitochondrial injury and Hapten's role are proposed to cause DILI. It can result in acute liver failure and even death if the suspected drug is not stopped. In India, antitubercular drugs are the major group of drugs known to cause DILI, apart from other antimicrobial drugs and NSAIDs. The International DILI Expert Working Group under CIOMS has put forward a grading system to assess severity of DILI based on clinical and laboratory findings. FDA evaluates hepatotoxicity of a drug before approval using Hy's rule, which states that 3 times elevation of Alanine aminotransferase (ALT) enzyme along with jaundice results in 5 to 50% fatality. The most useful approach for DILI detection and risk assessment is based on comprehensive hepatic data collection, assessment, and interpretation during clinical trials of drug development.

Keywords: *Drug induced liver injury, DILI, Hepatotoxicity, Live damage*

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INTRODUCTION

Liver, the initial site of contact for orally ingested xenobiotics, alcohol, and other substances, is highly susceptible to chemical-induced injury (Gu and Manautou, 2013) due to first pass metabolism. Normal biotransformation of nutrients and xenobiotics can result in generation of reactive oxygen species (ROS), which can be cleared off the system by endogenous cytoprotective mechanisms like antioxidant enzymes, Phase II conjugation, vitamin C and efflux transporters (Gu and Manautou, 2013). In some conditions, production of ROS is enhanced, and the activity of antioxidants is reduced resulting in oxidative stress (Cederbaum et al., 2009). Around 1000 drugs are responsible for DILI and it is the

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most frequent reason for withdrawal of approved medications from the market. DILI accounts for more than 50% of the cases of acute liver failure, with paracetamol being the principal offending agent (Abboud and Kalplowitz, 2007). A proper understanding of drugs implicated in clinical presentation, laboratory investigations and diagnosis of DILI is important.

METHODS

A structured search of bibliographic databases like PubMed, Google scholar and other online databases for articles on DILI was done for preparing this review.

DISCUSSION

DRUG INDUCED LIVER INJURY

Drug induced hepatotoxicity implies chemical induced liver damage, which can be due to overdose or even therapeutic dose of certain medicines, herbal remedies, some laboratory and industrial chemical agents, etc. Drug - induced hepatotoxicity is the most common reason for the culprit drug to be withdrawn from the market, with more than 900 drugs being implicated in causing the same. 5% of all hospital admissions and 50% of all acute liver failures are found to be drug induced, which can even result in liver transplantation or death (Ostapowicz et al., 2002).

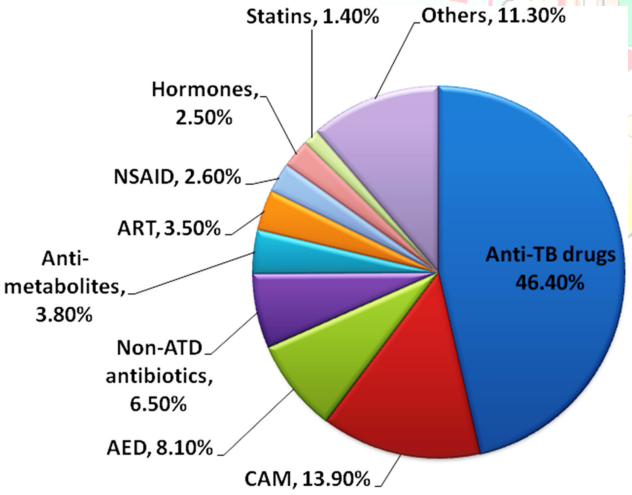

Fig. 1 Agents/Classes causing DILI (Adapted from Devarbhavi et al., 2021)

The U.S. Food and Drug Administration (FDA) has withdrawn several drugs from the market, including troglitazone, risperidone, trovafloxacin, and nefazodone, etc. owing to the significant hepatotoxicity associated with them (Holt et al., 2006). In September 2002, the Drug Controller General of India (DCGI) ordered a review for the drug Nimesulide in view of concerns of hepatotoxicity in paediatric age group and the review committee came up with the distrustful results (K C Singhal and S Z Rahman, 2003).

Drug Induced Liver Injury (DILI) involves any injury to the liver caused by a prescribed medication, over-the-counter medication, herbal preparation or dietary supplement which can start as asymptomatic liver enzyme elevation and can even end up as acute liver failure (Leise et al., 2014). A few drugs that come under DILI and their mechanisms are presented in Table 1.

Table 1: Types of drug induced liver injury and their mechanisms (Singh N et al., 2021)

LIVER PATHOLOGY	DRUGS	MECHANISM
Zonal necrosis	Paracetamol, CCL_4 Amatoxins	Inhibition of RNA synthesis→Cessation of protein synthesis confined to particular zone of the liver lobule
Cholestasis	Chlorpromazine, estrogen	Impairment of bile flow, itching and jaundice
Steatosis	Carbamazepine	Triglyceride accumulation
Non-alcoholic steatohepatitis	Didanosine, tetracycline, acetylsalicylic acid, valproic acid	Altered mitochondrial respiration, β- oxidation leads to lactic acidosis and triglyceride accumulation
Granuloma	Diltiazem, sulfa drugs, quinidine	Granulomas in periportal or portal areas
Vascular lesions	Nicotinic acid, cocaine, methylenedioxy methamphetamine	Injury to the vascular endothelium/ Causes ischemic or hypoxic injury
Oncogenesis	Oral contraceptives, androgens	Encourages tumor formation

Drug induced liver injury usually results from immunological response or due to direct biochemical interaction of metabolites (Kaplowitz, 2004). Liver, with its highest supply of biotransformation enzymes, metabolizes xenobiotics and renders them hydrophilic to make their excretion more efficient. During this process, short-lived, highly reactive intermediates like electrophiles, neutrophils and free radicals are formed which react with the functional groups and lead to adverse effects.

Different protective mechanisms are present in each cell for repair and removal of damaged protein, chemically altered DNA and peroxidised lipids (Gu and Manautou, 2013).

TYPES OF DILI

DIRECT OR TYPE A HEPATOTOXICITY

Intrinsic or Predictable drug reactions usually occur within a few days (Kaplowitz, 2004), characterized by serum enzyme elevation without jaundice such as by Paracetamol. This type of hepatotoxicity usually resolves spontaneously or once the drug is withdrawn or the dose is reduced and severe cases can lead to hepatic failure. Histopathology of the liver shows centrilobular or panlobular necrosis (Hoofnagle and Björnsson, 2019).

INDIRECT OR TYPE 2 HEPATOTOXICITY

Unpredictable drug reaction occurs after a latency of 1-8 weeks (intermediate) or upto 1 year (long) (Kaplowitz, 2004). Acute hepatocellular hepatitis is the most common manifestation of Indirect Hepatotoxicity with prominent

elevation in ALT without jaundice (Hoofnagle and Björnsson, 2019) such as by Phenytoin.

IDIOSYNCRATIC HEPATOTOXICITY

Immune mediated hepatic injury starts after 1-3 months of initiation of suspected drug therapy. Histology shows monocytic inflammatory infiltrates (Uetrecht J, 2019) such as Isoniazid, Diclofenac and Nitrofurantoin.

A 3 times elevation of the upper limit value of Alanine transaminase (ALT) levels is considered as a biochemical marker for liver injury. According to Hyman Zimmerman, elevated ALT accompanied by jaundice was associated with 5% - 50% mortality and this observation has since been referred to as "Hy's rule". This rule is currently used by the FDA in the evaluation of hepatotoxicity for newly developed drugs, before approval (Holt and Ju, 2006).

Various hypothesis and proposals for mechanism of DILI:

A. Immune mediated DILI

This hypothesis suggests that the immune system of susceptible individuals would more readily recognize the newly formed antigens. Both the innate immune system and adaptive immune response lead to liver damage. Lymphocytes are recruited to the liver in response to injury and inflammation, leading to destruction of hepatocytes and cholangiocytes, resulting in persistent tissue damage (Adams et al., 2010).

B. Mitochondrial injury

The reactive oxygen species generation and associated mitochondrial oxidative stress results in opening of mitochondrial permeability transition (MPT) pores through the direct toxicity or immune response leading to cell inflammation, apoptosis, and necrosis (Zheng et al., 2021).

C. Hapten hypothesis

Hapten hypothesis was suggested when antibodies against the drug modified hepatic proteins were detected in DILI patients. It is a type of drug induced adaptive immune response (Holt and Ju,2006).

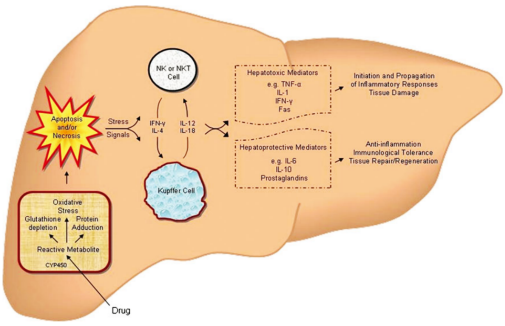

Fig. 2: Illustration of proposed mechanism of DILI: Adapted from Holt and Ju,2006

The following serum analytes were indicative of DILI once other causes of liver injury have been systematically excluded.

- ALT ≥ 5 times Upper Limit of Normal value (ULN).
- ALT ≥ 3 ULN, and total bilirubin > 2 ULN, and no or minimal elevations in ALP
- ALP ≥ 2 ULN when the source of increased ALP levels is the liver (Devarbhavi et al., 2021).

The Council for International Organizations of Medical Sciences (CIOMS) is the most reliable and widely used scale for determining causality in DILI. The international DILI expert working group has put forward the severity grading for DILI based on the clinical findings and laboratory investigations (Table no. 2).

It is worth mentioning here that two of the members (Dr. Hervé Le Louet, CIOMS / Henri Mondor University Hospital, Assistance Publique-Hôpitaux de Paris, France and Dr. Shanthi Pal, World Health Organization, Geneva, Switzerland) out of 34 CIOMS Working Group on Drug-Induced Liver Injury (DILI) has attended our annual conferences of the Society of Pharmacovigilance, India (SoPICON).

Syed Ziaur Rahman, Managing Editor, JPDS

Table-2: Severity Grading of DILI - International DILI expert working group

Grade 1 (Mild)	ALT ≥ 5 times ULN OR ALP ≥ 2 times ULN and TBL< 2 times ULN
Grade 2 (Moderate)	ALT ≥ 5 times ULN OR ALP ≥ 2 times ULN and TBL ≥ 2 times ULN or symptomatic hepatitis
Grade 3 (Severe)	ALT ≥ 5 times ULN OR ALP ≥ 2 times ULN and TBL ≥ 2 times ULN or symptomatic hepatitis AND At Least one of the following criteria - INR ≥ 1.5 - Ascites and/or encephalopathy - Duration of disease < 26 weeks - Other organ failure considered to be due to DILI
Grade 4 (Fatal/ Transplantation)	Death or liver transplantation due to DILI

ALT- Alanine aminotransferase **DILI-** Drug induced liver injury **INR-** international normalized ratio **ULN-** upper limit of normal range **TBL-** total serum bilirubin

(Adapted from CIOMS working group on drug-induced liver injury (DILI): consensus report, 2020, Page no.10)

CONCLUSION

DILI is one of the leading causes of acute and chronic liver injury and is being increasingly recognized for the challenges it poses to diagnosis and management. Diagnosis of DILI is challenging because of its relatively low incidence, varying clinical presentation, as well as the absence of specific biomarkers. Liver injury can be caused by many over-the counter medications and herbal remedies

and a failure to recognize DILI can result in need for liver transplantation and death. Pharmacovigilance, along with regular monitoring of ALT while on certain drugs are the important strategy for prevention of DILI.

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