International Journal of Current Trends in Pharmaceutical Research

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Review Article **Open Access**

Drug Induced Liver Injury: A Review Article

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A B S T R A C T

Drug-induced liver injury (DILI) is an important differential diagnosis in many patients in clinical hepatology. DILI is the primary cause of acute liver failure and is an important safety issue when new drugs are developed. The prime clinical presentation is acute hepatitis and/or cholestasis, even though almost any clinical pathological pattern of acute or chronic liver disease can occur. The pathogenesis of drug-induced liver disease usually involves the involvement of the parent drug or metabolites that either directly affect the cell biochemistry or elicit an immune response. Each hepatotoxin is associated with a characteristic signature regarding the pattern of injury and latency. However, some drugs may exhibit signature. Recent and future advances in toxicogenomics and proteomics should improve the identification of risk factors and the understanding of idiosyncratic hepatotoxicity.

Keywords: Drug induced liver injury, NSAIDS, Acetaminophen, Antibiotics.

A R T I C L E I N F O

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Article History: Received 31 October 2016, **Accepted** 27 November 2016, **Available Online** 15 January 2017

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Manuscript ID: IJCTPR3219

PAPER-QR CODE

Citation: Saritha Chandra, *et al.* Drug Induced Liver Injury: A Review Article. *Int. J. Curnt. Tren. Pharm, Res.*, 2017, 5(1): 45-48.

1. Introduction

Drug-induced liver toxicity is the most common cause of liver injury. It accounts for approximately one half of the cases of acute liver failure and imitates all forms of acute and chronic liver disease [1]. An estimated 1000 drugs have been implicated in causing liver disease on many occasions [2]. Although, with the exception of rare cases, drug-

induced liver injury subsides after termination of treatment with the drug, this represents an important diagnostic and therapeutic challenge for physicians [3]. DILI can be defined as a liver injury induced by a drug or herbal medicines leading to liver test abnormalities or liver dysfunction with reasonable exclusion of other competing etiologies. Most cases of DILI are due to idiosyncratic or unexpected reactions. Drug-induced liver disease (DILD) is a potential complication with many drugs. Acute hepatic injury due to drugs has been testified to occur in 5% to 10% of patients hospitalized for jaundice [4]. Moreover, drugs are the most common cause of hazardous hepatic failure, both in the United States and Europe. In reports from the United States and Sweden, distinctive drug reactions were the presumptive causes in 13% to 17% of cases of acute liver failure. The prognosis for patients with acute liver failure due to idiosyncratic drug reactions is usually poor, with 60% to 80% death rate without liver transplantation. During the last decade, drug-induced liver injury has led to the extraction of a number of drugs from the market [5]. The most important predictors of outcome in drug-induced liver disease with HC injury have not been analyzed in a large number of patients; furthermore, information about the prognosis in other forms of DILD (*e.g.*, DILD with cholestatic or mixed patterns) is limited.

2. Pathogenesis

The pathogenesis of drug-induced liver injury usually involves the participation of a toxic drug or metabolite that either elicits an immune response or directly affects the biochemistry of the cell.

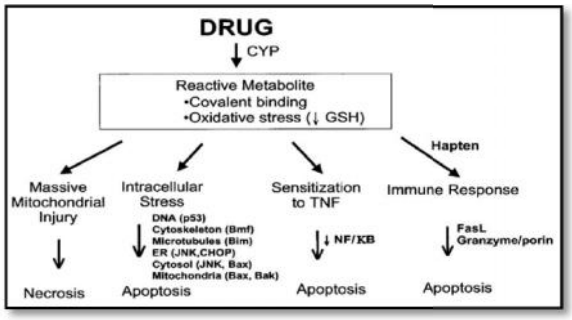

Figure 1: Cellular mechanisms of drug hepatotoxicity. Bmf, Bim, Bax, and Bak are proapoptotic members of the B cell lymphoma–2 protein family; CHOP, c/EBP homologous protein-10; GSH, glutathione; JNK, c-jun-N-terminal kinase; f, inhibition [1].

In either case, the resultant cell death is the event that leads to the clinical manifestation of hepatitis[1, 2]. Metabolism of chemicals takes place largely in the liver, which accounts for the organ's-dependent, susceptibility drug induced injury. The drug metabolites can be electrophilic chemicals or free radicals that undergo or promote a variety of chemical reactions, such as the depletion of reduced glutathione; covalently binding to proteins, lipids, or nucleic acids; or inducing lipid peroxidation (figure 1). All of these have consequent direct effects on organelles such as mitochondria, the endoplasmic reticulum, the cytoskeleton, microtubules, or the nucleus. They may also indirectly influence cellular organelles through the activation and inhibition of signaling kinases, transcription factors, and gene-expression profiles. The resultant intracellular stress leads to cell death caused by either cell shrinkage and nuclear disassembly (apoptosis) or swelling and lysis (necrosis)[1].Sensitization to liver-specific cytokines can also occur, thereby causing cytokine-induced hepatotoxicity[1,6]. Alternatively, the reactive metabolite may covalently bind to or alter liver proteins, such as cytochrome P450 enzymes, leading to an immune response and to immune-mediated injury[7,8]. This immune mediated, drug-induced hepatitis is usually characterized by fever, eosinophilia, or other allergic reactions that distinguish it from non–immune-mediated drug-induced hepatitis[9]. The mechanism for the induction of the immune-mediated drug reaction is not clear, but it may involve a hapten-like action[10]. Generally, low-molecular-weight organic chemicals or drugs are not immunogenic, but they may become so when they are bound to a macromolecule, such as a protein. If a drug metabolite produced by cytochrome P450 is able to act as a hapten, it would covalently bind to a liver protein and, subsequently, alter that protein[11]. This altered protein would then be perceived as foreign by the immune system, resulting in an autoimmune attack on normal hepatocellular constituents. This hypothesis, however, does not explain many aspects of immune-mediated drug-induced hepatitis. For instance, covalent binding (haptenation) is a regular occurrence with drugs, such as halothane, that rarely cause immune-mediated toxicity[12]. It is possible that a reactive metabolite may also have to injure or stress liver cells, in addition to modifying a protein, to induce an immune response[13]. Certain drugs exclusively or predominantly induce cholestasis.Several of these, such as sulindac[14] and chlorpromazine[15], are associated with hypersensitivity-type reactions. The specific immunological targets of these hypersensitivity type adverse reactions are poorly understood. However, given that the predominant histological features are portal inflammation and biliary injury, they are likely to be related to the bile duct. It is possible that toxic metabolites undergoing canalicular excretion react with macromolecules in the duct cells or undergo further metabolism within these cells, resulting in ductal injury [15]. Drug-induced immune-mediated injury, therefore, is an adverse immune response against the liver and/or bile duct that results in a disease with clinical features that are hepatic, cholestatic, or a mixture, the mechanisms of which are not clearly understood.

Presentation and clinical evaluation of DILI

Patients who suffer from DILI have a wide variety of clinical presentations. Clinically, biochemically and histologically, DILI can simulate almost all forms of acute and chronic liver injuries. Thus, these patients can present with acute liver failure with severe encephalopathy, with acute hepatitis with or without jaundice, and chronic hepatitis with both symptomatic and asymptomatic elevated liver tests. Table 2. Shows the spectrum of liver disease, with examples of drugs leading to different types of liver injury. Although rare, liver cirrhosis has been reported to

occur with long-standing drug treatment suspected to have caused DILI [16] a minority of patients with DILI (approximately 25–30%) present with symptoms suggestive of immune allergic drug reactions with fever, rash and eosinophilia.

Table 2: Most common types of liver injury that have been identified with drugs

Spectrum of DILI	Examples of drugs
Acute liver necrosis	Isoniazid, disulfiram, paracetamol
Chronic hepatitis	Phenytoin, isoniazid
Drug-induced AIH	Minocycline, Nitrofurantoin
Granulomatous hepatitis	Carbamazepine, quinidine
Steatohepatitis	Amiodarone, valproate
Cholestatic hepatitis	Flucloxacillin, amoxicillin/Cla
Bland cholestasis	Estrogens, Nimesulide
Ductopenia	Amoxicillin, Trimethoprim-sulpha
Fibrosis	Methotrexate
Nodular regenerative hyperplasia	Azathioprine, 6-thioguanine

3. Causative drugs

A very large number of different drugs have been associated with liver injury [2]. There is a clear difference in the documentation or the evidence for hepatotoxicity associated with these drugs. For some drugs, only a single case report or a letter to the editor indicating DILI is available. Other drugs have well-characterized hepatotoxicity, examples being isoniazid, phenytoin, disulfiram, amoxicillin/Clavulanate to mention a few. In early reports, halothane and chlorpromazine were commonly reported to be associated with hepatotoxicity More recently, antibiotics, different analgesics and NSAIDs are the most common type of drugs associated with DILI [17,16]. The most common antibiotics implicated have been amoxicillin, Clavulanate, sulpha anderythro Nitrofurantoin, but antituberculous drugs such as isoniazid and rifampicin have also been commonly observed in these series [18]. Type of drugs and specific drugs associated with DILI in different studies from the literature are shown in Table 3.

4. Management

Once DILI is suspected in patients with new-onset liver disease, prompt cessation of drug(s) implicated is usually the first step in their management. At the same time, severity assessment of the liver disease is of crucial importance. At the onset of the reaction, symptomatic patients with jaundice are in most cases hospitalized, and obviously, patients who also have coagulopathy and/or encephalopathy should be hospitalized. It is important to recognize the severity of the liver injury in a patient with jaundice and coagulopathy before the development of encephalopathy. Encephalopathy is a very late sign and after its development, a rapid deterioration is often observed. Thus, an early contact should be taken with a transplant centre if the patient does not have an obvious contraindication for liver transplantation. In paracetamol-induced liver failure, N-acetyl cysteine (NAC) should be given immediately [19]. Drug-induced liver disorders occur frequently, can be life threatening, mimic all forms of liver disease. However, except in rare cases of drug-induced chronic hepatitis and vanishing bile duct disease, the liver injury subsides and the adverse event disappears after the cessation of treatment with the drug.

The liver is a particular target for drug toxicity because of its role in clearing and metabolizing chemicals. The parent drug, or metabolite, may affect critical biochemical functions, sensitize the liver to the effects of cytokines, or elicit an immune response. This induced reaction is often unpredictable, which implies that other factors— such as environment, age, sex, and genetic factors are able to alter the susceptibility to the adverse event. Most drugs with predictable liver toxicity are screened out during preclinical drug development, but unpredictable and rare hypersensitivity or idiosyncratic reactions are often not noted until a drug is used in the clinical situation. A wide range of liver diseases can occur, but individual hepatotoxic drugs generally have a characteristic clinical and pathological signature and latency period. Most are similar to acute hepatitis, cholestasis or mixed presentation.

5. Conclusion

Drug-induced, immune mediated hepatic injury is an adverse immune response against the liver that also exhibits hepatic, cholestatic, or mixed clinical features. However, it should be noted that some drugs exhibit more than one signature reaction. Hepatotoxicity caused by drugs, in particular idiosyncratic reactions, is a major challenge to the pharmaceutical industry and physicians. The application of new technologies, such as pharmacogenomics, toxicogenomics, proteomics, and metabonomics, offers the potential to identify risk factors and clarify the pathogenesis of idiosyncratic hepatotoxicity. Pharmacogenomics holds promise in identifying the genetic polymorphisms associated with drug metabolism, toxicogenomics characterizes patterns of altered gene expression, proteomics characterizes patterns of altered protein expression, and metabonomics characterizes patterns of altered metabolites in urine or blood. These altered patterns can provide clues as to pathogenesis and define the molecular signature of the toxicity of a specific drug or groups of drugs by its mechanism of action or clinical manifestations. These technologies may be useful during drug development in predicting trouble during animal-model studies and in the post marketing assessment of idiosyncratic reactions.

6. Acknowledgement

I express my profound and sincere gratitude to my guide Saritha chandra, and Principal-jagan college of pharmacy for providing necessary facilities and offering valuable advice and meaningful support to carry out this work.

Table 2: Type of drugs and specific drugs associated with DILI in different studies from the literature

Reference	Origin (time period) n=number of Specific drugs	Types of drugs
Aithal and Day	UK (1978–1996) n = 44	Antibiotics (29.5%), NSAIDs (25%), dextropropoxyphene (9%), chlorpromazine (6.8%).
Sgro et al.	Spain (1993–1998) n = 103	Analgesics (28%), antibiotics (24%), H2-receptor antagonists (22%), benzodiazepines (16.5%), antidepressants (13.6%), herbs (11%), ACE inhibitors (11%), antituberculous drugs (11%)
Russo et al.	USA (1990–2002) n = 270	Paracetamol (46%), isoniazid (17.5%), anticonvulsants(15%), Propylthiouraci l(7.3%), antibiotics (10.2%), herbs(5.1%), disulfiram (4.4%).
De Abajo et al.	UK (1994–1999) n = 128	Antibiotics (27%), paracetamol alone or combined (9%), Diclofenac (8%), chlorpromazine (4.7%),
Meier et al.	Switzerland (1996–2000) n = 57	Heparins (45.6%), antibiotics (33%), anticancer drugs (12%) Amoxicillin (13%), antituberculous drugs (7%),
Andrade et al.	15 Spain (1994–2004) n = 446	Diclofenac (2.7%), Antibiotics (27%), NSAIDs (4.8%), disulfiram (3.4%).
De Valle et al.	Sweden (1995–2005) n = 77	Atorvastatin (5.2%), Analgesics (8.9%), HIV drugs (6.5%), anticonvulsants (3.9%), antibiotics (3.6%).
Bjornsson and Olsson39	Sweden (1968–2003) n = 4.690	Anticonvulsants (3.9%), antibiotics (3.6%) 30 Antimicrobials (45.5%), CNS agents (15%), medicinal immunomodulatory agents (5%), Antihypertensive (5%).
Aithal and Day	USA (2003–2008) n = 300	Antibiotics (29.5%), NSAIDs.

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