Mechanisms of Drug-Induced Hepatotoxicity

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KEYWORDS

• Hepatotoxicity • Reactive metabolites • Mitochondria • Hepatocellular • Cholestasis

KEY POINTS

- Drug-induced hepatotoxicity (DIH) is an important clinical problem and a leading cause of liver failure in adults.
- Multiple mechanisms and factors contribute to the etiology and pathology of DIH.
- Generation of reactive metabolites, oxidative stress, and mitochondrial dysfunction are common mechanisms of DIH.

Drug-induced hepatotoxicity (DIH) is an important clinical problem in the United States and around the world. It is one of the primary reasons for failure of drug candidates during preclinical drug development, early-phase clinical trials, and Food and Drug Administration drug withdrawal from the market after drug approval (examples in **Tables 1** and **2**).[1] Previous reports have shown that drug-mediated hepatotoxicity is responsible for more than 50% of reported cases of acute liver failure in the United States.[2] Although acetaminophen (APAP) accounts for a majority of cases of DIH, other drugs also account for acute liver failure more frequently than viral hepatitis and other causes.[2] In a population-based study in Iceland, the incidence of DIH was reported to be as high as 19 cases per 100,000 people.[3] DIH can present as acute liver failure or chronic liver failure, which makes it difficult to distinguish DIH from other liver diseases.

DIH usually appears as elevations of serum liver enzymes with or without an increase in bilirubin. DIH is defined as an increase in alanine aminotransferase (ALT) 5 times above the upper limit of normal or baseline value; alkaline phosphatase (ALP) 2 times above the upper limit of normal; or a combination of ALT 3 times above the upper limit of normal and bilirubin 2 times above the upper limit of normal.[4] The pattern of liver enzyme increase is further classified into 3 subtypes based on the R value, which is defined as the ratio of ALT to ALP expressed in multiples of the

The authors have nothing to disclose.

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Clin Liver Dis 21 (2017) 35–54
http://dx.doi.org/10.1016/j.cld.2016.08.002 **liver.theclinics.com**

Table 1
Drugs withdrawn from the market due to hepatotoxicity (United States, European Union, United Kingdom, and France)

Drug	Class	Mechanism of Toxicity
Troglitazone	Antidiabetic/anti-inflammatory	Reactive metabolites
Benoxaprofen	NSAID	Reactive metabolites
Bromfenac	NSAID	Reactive metabolites
Ibufenac	NSAID	Reactive metabolites
Temafloxacin	Fluoroquinoline antibiotic	Not clear
Alatrofloxacin	Fluoroquinoline antibiotic	Not clear
Trovafloxacin	Fluoroquinoline antibiotic	Mitochondrial dysfunction, inflammatory stress
Benzarone	Thrombolytic	Reactive metabolites
Ximelagatran	Anticoagulant	Immune mediated
Clomacron	Psychotropic drug	Not clear
Nafazodone	Antidepressant	Reactive metabolites
Cyclofenil	Antiestrogen	Not clear
Dilevalol	Antihypertensive	Immune mediated
Sitaxentan	Antihypertensive	Mitochondrial dysfunction Covalent binding to liver proteins
Tienilic acid	Antihypertensive	Reactive metabolites Immune response
Pemoline	CNS stimulant	Partly immune mediated Not completely clear

Abbreviations: CNS, central nervous system; NSAID, nonsteroidal anti-inflammatory drug.
Data from Refs.[115–119]

upper limit of normal. An R value greater than 5 denotes hepatocellular injury; R value of 2 to 5 is mixed; and R value less than 2 is cholestatic type of injury. Hepatocellular pattern of liver injury is characterized by cellular necrosis and inflammation with little or no elevation of bilirubin. ALT and aspartate aminotransferase (AST) levels are usually high whereas ALP levels are mildly increased. Patients usually present with malaise and exhaustion. The cholestatic pattern of injury is typified by accumulation of bile in the hepatocytes due an insult to the bile ducts, increased levels of bilirubin and ALP, and jaundice with itching on the skin. The mixed pattern of injury is often encountered in DIH and combines the features of hepatocellular and cholestatic pattern of liver injury. Patients may present with both exhaustion and itching, elevated levels of ALT and ALP, and bile accumulation. DIH can also appear in the form of other liver diseases, like acute or cholestatic hepatitis, steaotosis, acute necrosis, chronic hepatitis, and nonalcoholic fatty liver disease (http://livertox.nih.gov/Phenotypes_enzy.html).

DIH can be dose dependent and predictable or it can be idiosyncratic, which occurs only in specific individuals and is not strictly drug dose dependent. Many efforts have been made in understanding the mechanisms that drive DIH. General mechanisms involved in DIH include cell death, metabolism-mediated reactive metabolite formation, immune-mediated reaction, and mitochondrial dysfunction. Multiple mechanisms together seem to contribute to clinically observed DIH (**Fig. 1**).