DRUG INDUCED HEPATOTOXICITY - A REVIEW

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ABSTRACT
Liver is a major organ having different functions. It plays an important role not only in the metabolism, synthesis and storage but also in the detoxification of many endogenous and exogenous compounds and converting them to less toxic substances for excretion. Hepatotoxicity refers to chemical-driven liver damage. Certain medicinal agents when taken in overdoses and sometimes even when introduced within therapeutic ranges may injure the liver. The liver plays a central role in detoxifying chemicals and is susceptible to the toxicity from these agents. The present review provides an overview of drugs causing hepatotoxicity, various types of drug induced hepatotoxicity.

Key words: Liver; Hepatotoxins; Intrinsic; Idiosyncratic; Liver diseases

INTRODUCTION
Drugs are an important cause of liver injury. More than 1000 drugs and toxins have been reported to cause liver injury, and drugs account for 20-40% of all instances of fulminant hepatic failure. Approximately 75% of the idiosyncratic drug reactions result in liver transplantation or death. Drug-induced hepatic injury is the most common reason cited for withdrawal of an approved drug. Drugs used for the manifestation of various diseases account for over 50% of acute liver failure. Drugs account for 2-5% of cases of patients hospitalized with jaundice and approximately 10% of all cases of acute hepatitis.

Risk factors for drug-induced liver injury
• Race: Some drugs appear to have different toxicities based on race. For example, blacks and Hispanics may be more susceptible to isoniazid (INH) toxicity. The rate of metabolism is under the control of P-450 enzymes and can vary from individual to individual.
• Age: Apart from accidental exposure, hepatic drug reactions are rare in children. Elderly persons are at increased risk of hepatic injury because of decreased clearance, drug-to-drug interactions, reduced hepatic blood flow, variation in drug binding, and lower hepatic volume. In addition, poor diet, infections, and multiple hospitalizations are important reasons for drug-induced hepatotoxicity.
• Sex: Although the reasons are unknown, hepatic drug reactions are more common in females.

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• **Alcohol ingestion:** Alcoholic persons are susceptible to drug toxicity because alcohol induces liver injury and cirrhotic changes that alter drug metabolism. Alcohol causes depletion of glutathione (hepatoprotective) stores that make the person more susceptible to toxicity by drugs.

• **Liver disease:** In general, patients with chronic liver disease are not uniformly at increased risk of hepatic injury. Although the total cytochrome P-450 is reduced, some may be affected more than others. The modification of doses in persons with liver disease should be based on the knowledge of the specific enzyme involved in the metabolism. Patients with HIV infection who are co-infected with hepatitis B or C virus are at increased risk for hepatotoxic effects when treated with antiretroviral therapy. Similarly, patients with cirrhosis are at increased risk of decompensation by toxic drugs.

• **Genetic factors:** A unique gene encodes each P-450 protein. Genetic differences in the P-450 enzymes can result in abnormal reactions to drugs, including idiosyncratic reactions. Debrisoquine is an antiarrhythmic drug that undergoes poor metabolism because of abnormal expression of P-450-II-D6. This can be identified by polymerase chain reaction amplification of mutant genes. This has led to the possibility of future detection of persons who can have abnormal reactions to a drug.

• **Other co-morbidities:** Persons with AIDS, persons who are malnourished, and persons who are fasting may be susceptible to drug reactions because of low glutathione stores.

• **Drug formulation:** Long-acting drugs may cause more injury than shorter-acting drugs.

### Classification of drug induced liver disease

Drug-induced liver disease can be classified as intrinsic (predictable) and idiosyncratic (unpredictable).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intrinsic</th>
<th>Idiosyncratic</th>
</tr>
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<tbody>
<tr>
<td>Predictability</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Dose-dependence</td>
<td>Yes</td>
<td>No</td>
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**Intrinsic drug-induced liver disease**

Intrinsic (predictable) drug reactions can cause liver damage. Predictable drug-induced liver disease is related to the dosage of drugs that cause liver injury. Certain drugs have toxic effects on the liver in a dose-dependent manner. This kind of liver disease can be treated easily upon careful examination of the patient's drug history. Toxic doses of acetaminophen that result in hepatocellular necrosis is the most frequently recorded case of drug induced liver failure. Other drugs that cause different liver diseases are amiodarone, bromfenac, tetracycline, niacin, cyclosporine, and certain oral contraceptives.
Idiosyncratic Drug-induced Liver Disease

Idiosyncratic (unpredictable) drug reactions can cause liver injury. This type of drug reaction occurs mostly in persons who cannot tolerate a particular drug. Use of one particular drug may cause liver disease only in a fraction of individuals. It is not related to dosage, i.e., even small amounts of the drug can cause adverse reactions and are usually due to some genetic disorder. Enzymes required to metabolize certain drugs may not be present in liver cells causing damage to the liver. Isoniazid and diclofenac may cause hepatocellular necrosis. Drugs like chlorpromazine and estrogen may cause cholestasis. Use of certain oral contraceptives and anabolic steroids may result in hepatic or liver tumor.

Pathological manifestations of drug-induced liver injury

Based on the pattern of liver histology, the pathological manifestations of liver injury may be classified into categories as described below.

Acute hepatocellular injury

Manifestations of acute liver injury may range from spotty necrosis to fulminant liver failure. Spotty necrosis resembles classic viral hepatitis and involves all acinar zones. Hepatocellular injury consists of ballooning degeneration or apoptosis with eosinophils, especially in cases of peripheral eosinophilia. Drugs that can cause this type of injury are INH, halothane, phenylbutazone, indomethacin, and disulfiram \( \text{3-5} \). Submassive necrosis, as the name suggests, may affect zone 1 (periportal) or zone 3 (central necrosis). Periportal changes occur with ferrous sulfate poisoning, phosphorus poisoning, and cocaine toxicity. Central necrosis occurs with acetaminophen, halothane, methoxyflurane, trovafloxacin, ketoconazole, dihydralazine, tacrine, and mushroom poisoning. Massive necrosis is an extension of submassive necrosis and manifests as fulminant failure.

Chronic hepatocellular injury

Drug-induced chronic changes manifest many forms.

Pigment accumulation

Lipofuscin pigment storage in the liver cells has been reported with phenothiazines, phenacetin, aminopyrine, and cascara
Hemosiderin accumulation in the liver cells may result from excessive iron ingestion or parenteral iron therapy in patients undergoing hemodialysis.

**Steatosis, steatohepatitis, and phospholipidosis**

Steatosis secondary to drug toxicity may be in the form of medium-sized and large droplets (macrovesicular) or small droplets (microvesicular). Microvesicular steatosis is observed with alcohol, aspirin, valproic acid, amiodarone, piroxicam, stavudine, didanosine, nevirapine, and high doses of tetracycline. Drugs that can cause macrovesicular steatosis include alcohol, corticosteroids, methotrexate, minocycline, nifedipine, parenteral nutrition, and perhexiline maleate. Steatohepatitis has been reported with amiodarone, nifedipine, synthetic estrogens, and didanosine. Phospholipidosis results from lysosomal phospholipid storage secondary to inactivation of lysosomal phospholipases by drugs. Common causes are perhexiline maleate, amiodarone, total parenteral nutrition (TPN), trimethoprim-sulfamethoxazole, and chloroquine.

**Hepatic fibrosis and cirrhosis**

Most hepatic drug reactions of minimal-to-moderate severity are followed by recovery and no significant fibrosis. Any drug causing submassive hepatocellular injury may be followed by fibrosis, nodular regeneration, and cirrhosis. However, some agents produce an increase in collagen deposition, with minimal or absent features of necrosis or inflammation. Drugs leading to fibrosis include methotrexate, thorotrast, and heroin. Prolonged therapy with methotrexate, INH, perhexiline, and valproic acid may lead to cirrhosis.

**Acute cholestasis**

Cholestasis is defined as a reduction in bile flow resulting from reduced secretion or obstruction of the biliary tree. If any evidence indicates hepatocellular injury, it is called cholestatic hepatitis. Histology shows apoptotic bodies, small foci of necrosis, and, less often, ballooning with or without zone 3 necrosis. Bile accumulates in the cytoplasm of the liver cells, canaliculi, and Kupffer cells. Drugs that lead to a pure cholestatic reaction include anabolic steroids (eg, methyl testosterone, oxymetholone, fluoxymesterone) and contraceptive steroids. Drugs that can cause cholestatic hepatitis include erythromycin, azithromycin, ciprofloxacin, ofloxacin, ranitidine, cimetidine, phenytoin, gold salts, and terbinafine. Intrahepatic cholestasis may be accompanied by acute cholangitis and is observed in patients taking chlorpromazine, allopurinol, chlorpropamide, and hydralazine.

**Chronic cholestasis**

Histology shows chronic portal inflammation and degeneration of the bile duct referred to as progressive ductopenia or vanishing bile duct syndrome. Most cases of drug-induced cholestasis are followed by rapid clinical and biochemical recovery upon withdrawal of the drug. However, approximately 1% of patients may continue to
have abnormal liver test results and some may progress to a condition resembling primary biliary cirrhosis. Causes of intrahepatic cholestasis include chlorpropamide, amoxicillin-clavulanate, trimethoprim-sulfamethoxazole, carbamazepine, and TPN. Floxuridine causes intrahepatic and extrahepatic cholestasis 20, 21.

Granulomatous hepatitis

Most of these reactions consist of noncaseating epithelioid granulomas located in periportal or portal areas. This injury is usually transient and causes no sequelae. Drugs implicated include sulfonamide, sulfonylurea, phenytoin, quinidine, and hydralazine. Long-term use of mineral oil for constipation can cause lipogranulomas. Allopurinol is known to cause granulomas with a fibrin ring, whereas gold salts may lead to the formation of lipogranulomas with black pigment. Carbamazepine is a common cause of granulomatous hepatitis 22, 23.

Autoimmune hepatitis

Histology reveals active necroinflammatory lesions with prominent plasma cells. Females are affected more often than males. Autoimmune hepatitis manifests insidiously as fatigue, anorexia, weight loss, jaundice, ascites, portal hypertension, hepatomegaly, and splenomegaly 24, 25. The serology may be positive for ANA, anti–smooth muscle antibody (ASMA), or lupus erythematosus factor with elevated gamma globulin levels. Examples of commonly implicated drugs include methyldopa, minocycline, nitrofurantoin, dihydralazine, sulfonamides, and trazodone 26.

Neoplastic lesions

Focal nodular hyperplasia and hepatocellular adenomas have been well described since the advent of oral contraceptive steroids. Many agents are linked to malignant hepatic neoplasms, including angiosarcoma from thorium dioxide 27.

Vascular lesions/venoocclusive disease

Drugs can injure any component of the liver, including the sinusoids, hepatic veins, and hepatic arteries. Azathioprine has been associated with hepatic venoocclusive disease in patients with a renal transplant, bone marrow transplant, and on long-term treatment for inflammatory bowel disease. Alcohol, excess vitamin A, floxuridine, and dacarbazine may lead to venoocclusive disease with or without acinar zone 3 necrosis. Oral contraceptives can cause focal sinusoidal dilatations. Both contraceptives and anabolic steroids may lead to peliosis hepatitis, ie, extrasinusoidal blood-filled spaces 28, 29.

CONCLUSION

Thus the present review outlines the effect of various drugs that can affect liver in its own way. Hence familiarity about the drug induced liver toxicities and their mechanism will pave way for the discoveries of treatment drugs against various drug induced hepatotoxicities.

REFERENCES


