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Drug –induced liver injury: A review

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Abstract
The incidence of drug induced liver injury (DILI) is about 1/1000 to 1/10000 among patients who receive therapeutic drug doses. Drug induced hepatotoxicity is a major cause of acute and chronic liver disease. The severity of liver damage ranges from nonspecific changes in liver structure to acute liver failure, cirrhosis and liver cancer. Some common agents that can cause liver injury are acetaminophen, antibiotics, statins, INH and herbal drugs. Drug-induced hepatotoxicity can be categorized based on the pattern of liver enzyme alteration (hepatocellular, cholestatic or mixed pattern), the mechanism of hepatotoxicity (direct, immune mediated or idiosyncratic) and histologic findings on liver biopsy (steatosis or sinusoidal obstruction syndrome). Treatment options for DILI include discontinuing the drug, conservative measurements and liver transplantation in the case of non-acetaminophen induced hepatotoxicity.
Keywords: Hepatotoxicity, Acetaminophen, Antibiotics, Statins

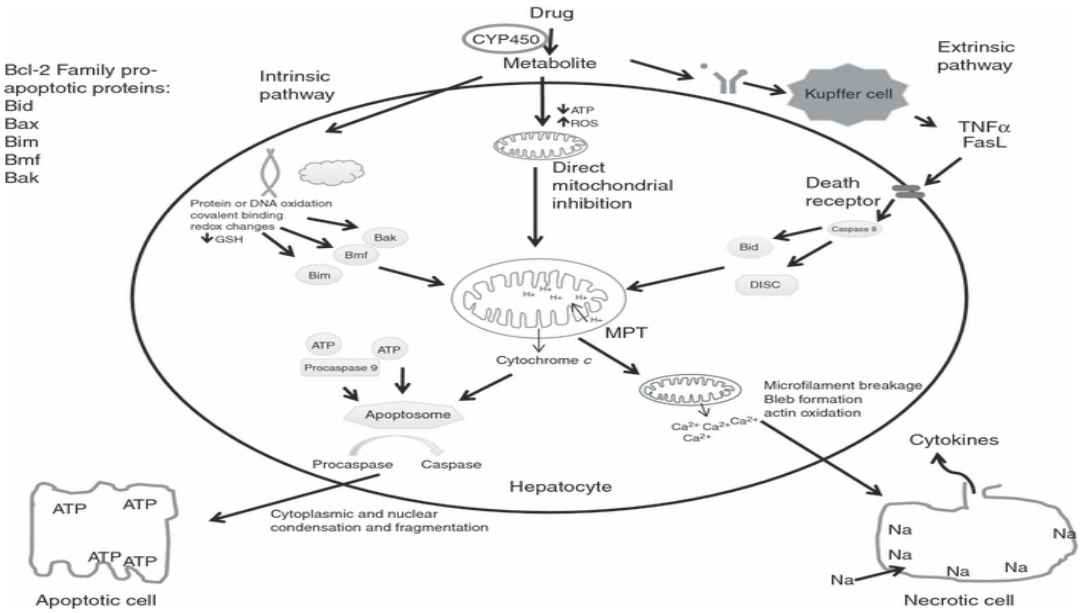
1. Introduction
Drugs are an important cause of liver injury. More than 900 drugs, toxins, and herbs have been reported to cause liver injury, and drugs account for 20-40% of all instances of fulminant hepatic failure. Approximately 75% of the idiosyncratic drug reactions result in liver transplantation or death. Due to under reporting and missed diagnoses, the incidence of DILI is probably higher than the reported range of one in 10 000 to one in 100 000 patients.[1] Only a minority of drugs have a predictable dose-dependent injury.

Rather, most drug induced liver injury (DILI) is thought to occur unpredictably, further contributing to the complexity of identifying and classifying DILI.[2] The rarity and unpredictability of injury events often lead to a drug's hepatotoxic potential being realized only after release into the marketplace, when many patients are exposed.[3][4]

The number of drugs associated with adverse reactions involving the liver is extensive.[5] One of the more common reasons for the withdrawal of a drug from the market place is an elevation of serum concentrations of liver enzymes.[6] Its impact on the pharmaceutical industry has led regulatory agencies to withdraw drugs from the market, restrict the use of certain medications, and issue black box warnings.[7] Alcohol-induced liver disease is the most common type of drug-induced liver disease.

2. Pathophysiology
The liver is often involved in drug toxicity due to its significant role in drug metabolism.[8] DILI is a multistep process that involves both direct drug injury and the subsequent activation of inflammatory pathways. This occurrence in a particular environmental setting and in combination with an individual's genetic susceptibility, establishes the milieu for the development of cellular and host injury.[9] The initial steps of injury are triggered by the offending drug, or more commonly, drug metabolites. The hepatotoxic metabolites are often the result of phase I drug metabolism and the polymorphic cytochrome P450 (CYP450) family of proteins. However, the toxic compounds may also arise from conjugative phase II metabolism.

Figure: 1



Injury from the drug is then propagated via subsequent cell stress, mitochondrial inhibition and/or specific immune reactions. Direct cell stress may be exerted through a variety of mechanisms including glutathione depletion or the binding of metabolites to enzymes, lipids, nucleic acids or other structures. Direct mitochondrial inhibition occurs through uncoupling or inhibition of the mitochondrial respiratory chain resulting in ATP depletion and accumulation of reactive oxygen species (ROS). [10]

Specific immune responses can be evoked through the binding of the drug or its metabolite to HLA proteins, which are then presented to T cells and recognized as antigens. The neo-antigens are subsequently placed on antigen presenting cells to activate formation of antibodies against themselves or activate the immune system to form auto-antibodies against cell structures.[11] Reactions are said to only occur in the presence of a second signal, which is commonly referred to as the 'danger signal'.[12] This signal is thought to activate signaling pathways for oxidative stress or cell damage resulting in immune-mediated liver damage. The signal may be a separate drug, host factor such as a viral or bacterial infection or a cytokine release from an inflammatory reaction.[13][14] A mild inflammatory reaction can often be the 'danger signal' that results in liver injury as shown in studies where low dose lipopolysaccharide enhanced the hepatotoxic potential of known hepatotoxic agents.[15]

Each of these pathways, be it cell stress, mitochondrial inhibition or immune activation, ultimately leads to mitochondrial permeability transition (MPT). MPT disrupts mitochondrial membranes by increasing permeability and proton influx through the inner membrane therefore disturbing ATP synthesis. This perturbation also causes mitochondrial matrix expansion and increased permeability of the outer mitochondrial membrane with release of cytochrome C and other pro-apoptotic proteins into the cell cytoplasm.[16]

Cell stress and immune reactions accomplish this in one of two ways. Cell stress initiates the direct pathway in which pro-apoptotic proteins are activated and anti-apoptotic proteins are inhibited to then activate MPT. Immune reactions activate the extrinsic pathway, where antigen presentation causes Kupffer cells to release TNFα and FAS ligand (FasL). TNFα and FasL then bind to intracellular death receptors and death domain proteins to activate caspase 8 resulting in the formation of the death-inducing signalling complex (DISC). Caspase 8 also activates the Bcl-2 pro-apoptotic proteins which, in conjunction with the DISC complex, lead to MPT.[8][17]

The final step of injury involves either cellular apoptosis or necrosis. Apoptosis is an ATP-dependent pathway and can only occur if MPT does not occur rapidly and simultaneously in all cellular mitochondria. When ATP is present, the cytochrome C will bind a cytoplasmic scaffold protein and pro-caspase 9 to form an apoptosome, which serves to activate caspases resulting in cytoplasmic and nuclear condensation and fragmentation. The fragments are then removed by phagocytosis. The process of apoptosis occurs without loss of plasma membrane integrity, which greatly decreases inflammation causing minimal secondary damage.[16]

Necrosis is the result of severely compromised mitochondrial function by MPT and depletion of ATP. The result is severe disruption of cell processes, which is followed by bleb formation, actin oxidation, microfilament breakage, cellular swelling and eventually plasma membrane rupture.[17]

3. Risk factors

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.

Alcohol ingestion: Alcohol causes depletion of glutathione (hepatoprotective) stores that make the person more susceptible to toxicity by drugs.

Liver disease: Preexisting liver disease has not been thought to make patients more susceptible to drug-induced liver injury,[19,20] but it may be that a diminished liver reserve or the ability to recover could make the consequences of injury worse. Although the total cytochrome P-450 is reduced in chronic liver disease, some may be affected more than others.

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.

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

Host factors that may enhance susceptibility to drugs, possibly inducing liver disease

- Female - Halothane, nitrofurantoin, sulindac
- Male - Amoxicillin-clavulanic acid (Augmentin)
- Old age - Acetaminophen, halothane, INH, amoxicillin-clavulanic acid
- Young age - Salicylates, valproic acid
- Fasting or malnutrition - Acetaminophen
- Large body mass index/obesity - Halothane
- Diabetes mellitus - Methotrexate, niacin
- Renal failure - Tetracycline, allopurinol
- AIDS - Dapsone, trimethoprim-sulfamethoxazole
- Hepatitis C - Ibuprofen, ritonavir, flutamide
- Preexisting liver disease - Niacin, tetracycline, methotrexate

3. Patterns of drug-induced liver disease

3.1 Hepatocellular injury

Hepatocellular injury is characterized by significant elevations in the aminotransferases in serum which usually precede elevations in total bilirubin levels and alkaline phosphatase levels.5 Acarbose, allopurinol, fluoxetine, and losartan are capable of causing hepatocellular injury.[21] Hepatocellular injuries can be further subdivided by specific histologic patterns and clinical presentations. Centrolobular necrosis, steatohepatitis (steatonecrosis), phospholipidosis, and generalized hepatocellular necrosis.

3.2 Centrolobular Necrosis

Centrolobular necrosis is often a dose-related, predictable reaction secondary to drugs such as acetaminophen; however, it also can be associated with idiosyncratic reactions, such as those caused by the anesthetic halothane. Also called direct or metabolite-related hepatotoxicity,

centrolobular necrosis is usually the result of the production of a toxic metabolite. The damage spreads outward from the middle of a lobe of the liver. Mild drug reactions, involving only small amounts of parenchymal liver tissue, may be detected as asymptomatic elevations in the serum aminotransferases.

More severe forms of centrolobular necrosis are accompanied by nausea, vomiting, upper abdominal pain, and jaundice.[22][23] these reactions are predictable, often dose-related effects in the liver caused by specific agents. When taken in overdose, acetaminophen becomes bioactivated to a toxic intermediate known as Nacetyl- p-benzoquinone imine (NAPQI). NAPQI is very reactive, with a high affinity for sulfhydryl groups. The amino acid glutathione provides a ready source of available sulfhydryl groups within the hepatocyte. When the liver's glutathione stores are depleted and there are no longer sulfhydryl groups available to detoxify this metabolite, it begins to react directly with the hepatocyte.

Replenishing the liver's sulfhydryl capacity through the administration of Nacetylcysteine early after ingestion of the overdose halts this pro-cess.[24][25] During the first hours after ingestion, some patients report mild symptoms of nausea and vomiting, but no elevations of the commonly measured liver enzymes are seen. Not for 40 to 50 hours after ingestion do serum elevations in the liver enzymes begin.[26]

3.2 Steatohepatitis

Steatohepatitis (also known as steatonecrosis) is a specialized type of acute necrosis resulting from the accumulation of fatty acids in the hepatocyte. Drugs or their metabolites that cause steatonecrosis do so by affecting fatty-

acid oxidation within the mitochondria of the hepatocyte. Hepatic vesicles become engorged with fatty acids, eventually disrupting the homeostasis of the hepatocyte. Alcohol is the drug that most commonly produces steatonecrotic changes in the liver. When alcohol is converted into acetaldehyde, the synthesis of fatty acids is increased.[27][28] When the hepatocyte has become completely engorged with microvesicular fat, it often breaks open, spilling into the blood.

If enough hepatocytes break open, an inflammatory response begins. If the offending agent is withdrawn before significant numbers of hepatocytes become necrotic, the process is completely reversible without long-term sequelae. In nonalcoholic steatohepatitis, the same end point is often achieved through oxidation of lipid peroxidases.[29] Tetracycline produces steatohepatitis and steatosis.[30] Sodium valproate also can produce steatonecrosis through the process of bioactivation. Cytochrome P450 converts valproate to delta-4-valproic acid, a potent inducer of microvesicular fat accumulation.[31]

Patients experiencing steatohepatitis may present with abdominal fullness or pain as their only complaint. Patients with more severe steatonecrosis will present with all the symptoms characteristic of alcoholic hepatitis such as nausea, vomiting, steatorrhea, abdominal pain, pruritus, and fatigue.

3.4 Phospholipidosis

Phospholipidosis is the accumulation of phospholipids instead of fatty acids. The phospholipids usually engorge the lysosomal bodies of the hepatocyte.[32] Amiodarone is associated with this reaction. Patients treated with amiodarone who develop overt hepatic disease tend to have received higher doses of the drug. These patients also have higher amiodarone–to–N-desethyl-amiodarone ratios, indicating a greater accumulation of the parent compound. Amiod aroneand its major metabolite N-desethyl-amiodarone remains in the liver of all patients for several months after therapy is stopped. The patient can present with either elevated aminotransferases or hepatomegaly; jaundice is rare.[33][34]

3.5 Generalized Hepatocellular Necrosis

Generalized hepatocellular necrosis mimics the changes associated with the more common viral hepatitis. The onset of symptoms is usually delayed as much as a week or more after exposure to toxin. Bioactivation is often important for toxic hepatitis to develop, but may not be the immediate cause of damage.

Many drugs that are associated with toxic hepatitis produce metabolites that are not inherently toxic to the liver. Instead, they act as haptens, binding to specific cell proteins and inducing an autoimmune reaction. The rate of bioactivation can vary between males and females and between individuals of the same sex.[35][36] The cytochrome P450(CYP450) system tends to metabolize lipophilic substrates that are actively pumped into the hepatocyte by an organic anion (or cation) transporting protein. The CYP450 subspecies 2C, 2D, 3A, and 4A are regulated by the highly inducible xenobiotic receptor on complementary DNA. The receptor is found in the liver, and to a lesser extent in the cells lining the intestinal tract, and is responsible for cholesterol catabolism and bile acid homeostasis.

The activity of this receptor is subject to genetic polymorphism as well. This results in a wide variation in the sensitivity of the population to generalized hepatocellular necrosis and other forms of hepatic damage.[37] Yet severe toxic hepatitis develops in only 1% or less of this population.[38] The N-acetyltransferase 2 (NAT2) genotype appears to play a role in determining a patient's relative risk. In one study, patients with the slow-type NAT2 genotype had a 28-fold greater risk of developing serum aminotransferase elevations than did patients with the fasttype NAT2 genotype.[39]

Isoniazid is metabolized by several pathways, acetylation being the major pathway. It is acetylated to acetylisoniazid, which, in turn, is hydrolyzed to acetylhydrazine.[40] Ketoconazole produces generalized hepatocellular necrosis or milder forms of hepatic dysfunction in 1% to 2% of patients treated for fungal infections. This reaction is fatal in high numbers of patients who are infected with the human immunodeficiency virus. In immune-compromised patients in whom ketoconazole is used for long periods of time, special care should be taken to watch for changes in liver function.[41]

3.6 Toxic Cirrhosis

The scarring effect of hepatitis in the liver leads to the development of cirrhosis. Some drugs tend to cause such a mild case of hepatitis that it may not be detected. The patient eventually presents not with hepatitis, but with cirrhosis. Methotrexate causes periportal fibrosis in most patients who experience hepatotoxicity. The lesion results from the action of a bioactivated metabolite produced by CYP450.30 this process occurs most commonly in patients treated for psoriasis and arthritis. The extent of damage can be reduced or controlled by increasing the dosage interval to once weekly or by routine use of folic acid supplements.[42] Vitamin A be normally stored in liver cells, and causes significant hypertrophy and fibrosis when taken for long periods in high doses. Hepatomegaly is a common finding, along with ascites and portal hypertension. In patients with vitamin A toxicity, gingivitis and dry skin are also very common. This is accelerated by ethanol, which competes with retinol for aldehyde dehydrogenase.[43]

3.7 Cholestatic Injury

A second pattern of hepatic damage is an injury that primarily involves the bile canalicular system and is known as cholestatic injury. In cholestatic disease, disturbance of the subcellular actin filaments around the canaliculi prevents the movement of bile through the canalicular system.[42] The inability of the liver to remove bile causes intrahepatic accumulation of toxic bile acids and excretion products.[44] Drug-induced cholestasis can occur as an acute disorder (e.g.,cholestasis with or without hepatitis and cholestasis with bile duct injury) or as a chronic disorder (e.g., vanishing bile duct syndrome, sclerosing cholangitis, and cholelithiasis).[45] However, the most common form of drug-induced cholestasis is cholestasis with hepatitis. Most patients with this acute disorder present with nausea, malaise, jaundice, and pruritus. Elevations in serum alkaline phosphatase levels are more prominent and usually precede the elevations of other liver enzymes in serum. Although the antipsychotic drug chlorpromazine appears to be the prototype drug for this disorder, other medications are associated with other forms of cholestatic injury, such as erythromycin estolate, amoxicillin clavulanic acid, and carbamazepine.[46] Canalicular cholestasis is often associated with long-term high-dose estrogen therapy. Clinically, these patients are often asymptomatic and present with mild to moderate elevations of serum bilirubin.[47]

Patients with low serum albumin concentrations may be at greater risk than patients with normal serum albumin concentrations. This reaction also has been reported to occur rarely with sulfonamides, sulfonylureas, erythromycin estolate and ethylsuccinate, captopril, lisinopril, and other phenothiazines.[48]

3.8 Mixed hepatocellular and Cholestatic injury:

In some patients, an injury may begin as hepatocellular (or cholestatic) and simply spread so rapidly that by the time the patient presents for diagnosis and treatment, all areas of the liver are affected. In other patients, the underlying mechanism of damage is such that cells are injured regardless of their anatomical location or primary metabolic role.

3.9 Liver Vascular Disorders

Focal lesions in hepatic venules, sinusoids, and portal veins occur with various drugs. The most commonly associated drugs are the cytotoxic agents used to treat cancer, the pyrrolizidine alkaloids, and the sex hormones. A centralized necrosis often follows and can result in cirrhosis. Azathioprine and herbal teas that contain comfrey (a source of pyrrolizidine alkaloids) are associated with the development of venoocclusive disease. Peliosis hepatitis is a rare type of hepatic vascular lesion that can be seen as both an acute and a chronic disease. The liver develops large, blood-filled lacunae (space or cavity) within the parenchyma. Rupture of the lacunae can lead to severe peritoneal hemorrhage. Peliosis hepatitis is associated with exposure of the liver to androgens, estrogens, tamoxifen, azathioprine, and danazol. Androgens with a methyl alkylation at the 17-carbon position of the testosterone structure are the most frequently reported agents that cause peliosis hepatitis, usually after at least 6 months of therapy.[49]

4. Diagnosis

History: History must include dose, route of administration, duration, previous administration, and use of any concomitant drugs, including over-the-counter medications and herbs. Knowing whether the patient was exposed to the same drug before may be helpful. The latency period of idiosyncratic drug reactions is highly variable; hence, obtaining a history of every drug ingested in the past 3 months is essential.

Onset: The onset is usually within 5-90 days of starting the drug.

Exclusion of other causes of liver injury/cholestasis: Excluding other causes of liver injury is essential.

Dechallenge: A positive dechallenge is a 50% fall in serum transaminase levels within 8 days of stopping the drug. A positive dechallenge is very helpful in cases of use of multiple medications.

Rechallenge: Deliberate rechallenge in clinical situations is unethical and should not be attempted; however, inadvertent rechallenge in the past has provided valuable evidence that the drug was indeed hepatotoxic.

5. Treatment & Management

Early recognition of drug-induced liver reactions is essential to minimizing injury. Monitoring hepatic enzyme levels is appropriate and necessary with a number of agents, especially with those that lead to overt injury. For drugs that produce liver injury unpredictably, biochemical monitoring is less useful. ALT values are more specific than AST values.

No specific treatment is indicated for drug-induced hepatic disease. Treatment is largely supportive and based on symptomatology. The first step is to discontinue the suspected drug. Specific therapy against drug-induced liver injury is limited to the use of N -acetylcysteine in the early phases of acetaminophen toxicity. L-carnitine is potentially valuable in cases of valproate toxicity. In general, corticosteroids have no definitive role in treatment. They may suppress the systemic features associated with hypersensitivity or allergic reactions. Management of protracted drug-induced cholestasis is

similar to that for primary biliary cirrhosis. Cholestyramine may be used for alleviation of pruritus. Ursodeoxycholic acid may be used. Lastly, consulting a hepatologist is also helpful.

5.1 Referral to liver transplantation center/surgical care

No specific antidote is available for the vast majority of hepatotoxic agents. Emergency liver transplantation has increasing utility in the setting of drug-induced fulminant hepatic injury. Considering early liver transplantation is important. The Model for End-Stage Liver Disease score can be used to evaluate short-term survival in an adult with end-stage liver disease. The parameters used are serum creatinine, total bilirubin, international normalized ratio, and the cause of the cirrhosis.

5.2 Monitoring:

The serum transaminases AST and ALT are the most commonly used transaminases in the clinical setting. There are often no set rules available for a particular drug. Concentrations of these enzymes should be obtained approximately every 4 weeks, depending on the reported characteristics of the reaction in question. Methotrexate should be monitored every 4 weeks, because toxicity usually develops over a period of several weeks to months.[50] In addition, some recommend that sulfobromophthalein or indocyanine-green excretion studies be performed on a regular basis and that patients treated for very long periods of time should have a liver biopsy performed every 12 months.[51]

6. Conclusion

Drug-induced liver injury remains a diagnostic challenge. Multicentre studies and international collaborative work involving well-characterized patients will increase our understanding of liver injury associated with drugs. New therapies for acute liver failure resulting from drugs are needed.

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