Different types of hepatotoxicities induced by drugs

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Abstract
In this article we are providing a theoretical background for understanding different types of hepatotoxicities induced by drugs. Drug induced hepatotoxicity a potential complication of nearly every medication that is prescribed, because the liver is central to the metabolic disposition of virtually all drugs and foreign substances. Although drugs are metabolised without injury to the liver, many fatal and near fatal drug reactions occur each year. More than 900 drugs have been implicated in causing liver injury and it is the most common reason for a drug to be withdrawn from the market.

Keywords: Hepatotoxicity, Hepatic dysfunction, Jaundice, Liver failure.

Hepatotoxicity
Hepatotoxicity implies chemical-driven liver damage. Certain medicinal agents, when taken in overdoses and sometimes even when introduced within therapeutic ranges, may injure the organ. Other chemical agents, such as those used in laboratories and industries, natural chemicals (e.g., microcystins) and herbal remedies can also induce hepatotoxicity. Chemicals that cause liver injury are called hepatotoxins. More than 900 drugs have been implicated in causing liver injury and it is the most common reason for a drug to be withdrawn from the market. Chemicals often cause subclinical injury to liver which manifests only as abnormal liver enzyme tests. Drug induced liver injury is responsible for 5% of all hospital admissions and 50% of all acute liver failures. More than 75 percent of cases of idiosyncratic drug reactions result in liver transplantation or death.

Pathophysiology of hepatotoxicity
Pathophysiologic mechanisms
The pathophysiologic mechanisms of hepatotoxicity are still being explored and include both hepatocellular and extracellular mechanisms. The following are some of the mechanisms that have been described:

Disruption of the hepatocyte
Covalent binding of the drug to intracellular proteins can cause a decrease in ATP levels, leading to actin disruption. Disassembly of actin fibrils at the surface of the hepatocyte causes blebs and rupture of the membrane.

Disruption of the transport proteins
Drugs that affect transport proteins at the canalicular membrane can interrupt bile flow. Loss of villous processes and interruption of transport pumps such as multidrug resistance–associated protein 3 prevent the excretion of bilirubin, causing cholestasis.

Cytolytic T-cell activation
Covalent binding of a drug to the P-450 enzyme acts as an immunogen, activating T cells and cytokines and stimulating a multifaceted immune response.

Apoptosis of hepatocytes
Activation of the apoptotic pathways by the tumor necrosis factor-alpha receptor of Fas may trigger the cascade of intercellular caspases, which results in programmed cell death.

Mitochondrial disruption
Certain drugs inhibit mitochondrial function by a dual effect on both beta-oxidation energy production by inhibiting the synthesis of nicotinamide adenine dinucleotide and flavin adenine dinucleotide, resulting in decreased ATP production.

Bile duct injury

Toxic metabolites excreted in bile may cause injury to the bile duct epithelium.

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Hepatitis

Hepatitis is an inflammation of the liver. The condition can be self-limiting or can progress to fibrosis (scarring), cirrhosis or liver cancer. Hepatitis viruses are the most common cause of hepatitis in the world but other infections, toxic substances (e.g. alcohol, certain drugs), and autoimmune diseases can also cause hepatitis.

These are the drugs which cause hepatitis as hepatotoxicity: Propyl thiouracil, Ethanol, Quinidine, Methyldopa, Nitrofurantoin, Oxacillin, Naficillin, Erythromycin, Isoniazid, Rifampin, Ethionamide, Rifabutin, Nevirapine, Paraldehyde, Indomethacin, Gold, Valproic Acid.

Cholestatic Jandice

Conjugated hyperbilirubinemia due to any form of hepatobiliary disease is essentially the result of impairment in bile formation and/or bile flow, a condi tion known as cholestasis. Cholestatic jaundice is often accompanied by a broad spectrum of laboratory, clinical, and histological abnormalities. Laboratory abnormalities include increased serum levels of alkaline phosphatase and gamma-glutamyltransferase (GGT), and variable elevation of bilirubin, serum copper, ceruloplasmin, cholesterol, lipoprotein X, and serum bile acids, as well as of prothrombin time, which is corrected by vitamin K supplementation.

These are the drugs responsible for cholestatic jaundice as hepatotoxicity Tolbutamide, Acetohexamide, Talazamide, Chlorpropamide, Nitrofurantoin, Ethchlorvynol, Thiabendazole.

Hepatic Necrosis

The clinical course of hepatic necrosis resembles an acute, toxic injury to the liver with sudden and precipitous onset, marked elevations in serum aminotransferase levels, and early signs of hepatic (or other organ) dysfunction or failure despite minimal or no jaundice.

These are the drugs responsible for hepatic necrosis as hepatotoxicity Halothane, Sulfisoxazole, Sulfamethoxazole, Sulfadiazine, Sulfasalazine, Sulfacetamide, Silver Sulfadiazine, Sulfadoxine, Pyrazinamide, Dapsone, Sufoxone Sodium, Arsenic, Ethclorvynol.

Cirrhosis

Cirrhosis develops when scar tissue replaces normal, healthy tissue in your liver. It happens after the healthy cells are damaged over a long period of time, usually many years. The scar tissue makes the liver lumpy and hard, and after a while, the organ will start to fail. The scar tissue makes it tough for blood to get through a large vein (the portal vein) that goes into the liver. When blood backs up into the portal vein, it can get into your spleen and cause trouble in that organ, too.

These are the drugs which cause cirrhosis as hepatotoxicity Ethanol, Losartan, Candesartan, Irbesartan, Valsartan, Telmisaltan, Eprosortan, Arsenic.

Elevation of Hepatic Enzymes

Elevated liver enzymes may indicate inflammation or damage to cells in the liver. Inflamed or injured liver cells leak higher than normal amounts of certain chemicals, including liver enzymes, into the bloodstream, which can result in elevated liver enzymes on blood tests. The specific elevated liver enzymes most commonly found are:

Alanine transaminase (ALT)

Aspartate transaminase (AST) these are the drugs which cause elevation of hepatic enzymes and hepatotoxicity occurs.

Phenytoin, Carbamazepine, Valproic Acid, Tacrine, Heparin, Mevastatin, Lovastatin, Simvastatin, Pravstatin, Fluvastatin, Atorvastatin, Cerivastatin, Niacin, Clofibrate, Flucytosine, Didanosine, Nevirapine, Delavirdine, Pentamidine, Methotrexate, Cytarabine, Gemcitabine, Vinorelbine, Irinotecan, Succimer, Sulindac, Diclofenac Zileuton

Hepatic Failure

When your liver is damaged, you may suffer from hepatic, or liver, failure. Exposure to viruses or harmful chemicals can harm the liver. In those with liver damage, the liver may eventually stop functioning

correctly. Liver failure is an extremely serious condition, and you should receive treatment immediately.

These are the drugs which are responsible for hepatic failure as hepatotoxicity Propylthiouracil, Halothane, Tolcapone, Niacin, Trovafloxacin, Itraconazole Fluconazole, Dilavirdive.

Jaundice

Jaundice is a yellow discoloration of the skin, mucous membranes, and the whites of the eyes caused by increased amounts of bilirubin in the blood. Jaundice is a sign of an underlying disease process. Bilirubin is a by-product of the daily natural breakdown and destruction of red blood cells in the body. The hemoglobin molecule that is released into the blood by this process is split, with the heme portion undergoing a chemical conversion to bilirubin. Normally, the liver metabolizes and excretes the bilirubin in the form of bile. However, if there is a disruption in this normal metabolism and/or production of bilirubin, jaundice may result.

These are the drugs responsible to cause jaundice as hepatotoxicity Chlorpromazine, Amitryptyline, Clomipramine, Doxepine, Imipramine, Trimipramine, Amoxapine, Desipramine, Maprotiline, Nortriptyline, Protriptyline, Sulfisoxazole, Sulfamethoxazole, Sulfadiazine, Sulfasalazine, Sulfacetamide, Silver Sulfadiazine, Sulfadoxine, Co-trimoxazole, Erythromycin, Isonioazid, Pyrazinamide, Dapsome, Sufoxone sodium, Sodium, Albendazole, Mercaptopurine, Indomethacin.

Hepatic Dysfunction

This is different to liver disease in that the liver has not yet sustained permanent or sufficient damage to cause gross impairment of its vital functions. In those with a dysfunctional liver, the routine blood tests of liver function are generally normal. A dysfunctional liver is not working efficiently, and is overloaded, toxic or sluggish. Liver dysfunction is much more common than liver disease, and may be a forerunner to liver disease.

These are the drugs which cause hepatic dysfunction Amiodarone, Methyldopa, Heparin, Sulfisoxazole, Sulfamethoxazole, Sulfadiazine, Sulfasalazine, Sulfacetamide, Silver Sulfadiazine, Sulfadoxine, Foscarnet, Ganiciclovir, Valganciclovior, Didanosine, Delavirdine, Melphalan, Cytarabine, Pentostatin, Flutamide, Interleukin-2.

Hepatomegaly

"Hepatic" refers to the liver and "megaly" refers to an increase in size. Hepatomegaly is a medical term which means an increase in the size of the liver. The factors that affect the size of the liver are age, gender, body weight and body shape. A liver that is 3 centimeters larger or smaller is still considered normal. If enlarged beyond the normal limits, it is good to get a medical evaluation done to find the underlying cause.

These are drugs which are responsible for hepatomegaly Sulfisoxazole, Sulfamethoxazole, Sulfadiazine, Sulfasalazine, Sulfacetamide, Silver sulfadiazine, Sulfadoxine, Allopurinol.

Hepatic Veno occlusive Disease

In hepatic veno occlusive disease blood flow is blocked only in very small blood vessels in the liver rather than in larger ones in the liver or in blood vessels outside the liver. That is, blockages do not affect the large hepatic veins and the inferior vena cava (the large vein that carries blood from the lower parts of the body, including the liver, to the heart). Veno-occlusive disease may occur at any age.Because flow out of the liver is blocked, blood backs up in the liver. This backup (congestion) then reduces the amount of blood entering the liver. Liver cells are damaged because they do not get enough blood (ischemia). The congestion causes the liver to become engorged and enlarged. The congestion also causes increased pressure in the portal vein (portal hypertension). Portal hypertension can result in dilated, twisted (varicose) veins in the esophagus (esophageal varices). The elevated pressure in the portal vein and the liver congestion lead to fluid accumulating in the abdomen—called ascites. The spleen also tends to enlarge.Such congestion reduces blood flow into the liver. The resulting liver damage leads eventually to severe scarring (cirrhosis).

These drugs are responsible for hepatic veno occlusive disease Mechlorethamine, Cyclophosphamide, Ifosamide, Chlorambucil, Melphalan, Thio-TEPA, Busulfan, Carmustine, Lomustine, Dacarbazine.

Hepatic Carcinogen

Hepatocellular carcinoma occurs most commonly in the setting of cirrhosis, where the annual rate of cancer development approximates 3-7%. Most cases arise in the setting of impaired liver regeneration combined with chronic inflammation and fibrosis. Liver progenitor cells play an important role in cell renewal processes in the liver in the setting of chronic injury and have recently emerged as potential candidates in the carcinogenic pathway. There are two main hypotheses which have been proposed to explain hepatocellular carcinogenesis, namely the de-differentiation and the maturation arrest hypotheses. Understanding the carcinogenic pathways and the role of liver progenitor cells will provide greater understanding and novel approaches to preventative strategies.

This drug is responsible for hepatic carcinogen Tamoxifen

Hepatic Encephalopathy

Hepatic encephalopathy is a syndrome observed in patients with cirrhosis. Hepatic encephalopathy is defined as a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction, after exclusion of brain disease. Hepatic encephalopathy is characterized by personality changes, intellectual impairment, and a depressed level of consciousness. An important prerequisite for the syndrome is diversion of portal blood into the systemic circulation through portosystemic collateral vessels. Hepatic encephalopathy is also described in patients without cirrhosis with either spontaneous or surgically created portosystemic shunts. The development of hepatic encephalopathy is explained, to some extent, by the effect of neurotoxic substances, which occurs in the setting of cirrhosis and portal hypertension

These are drugs which cause hepatic encephalopathy Acetazolamide, Dichlorphenamide, Methazolamide.

Hepatic Injury

Hepatic injury can result from blunt or penetrating trauma. Patients have abdominal pain, sometimes radiating to the shoulder, and tenderness. Diagnosis is made by CT or ultrasonography. Treatment is with observation and sometimes surgical repair; rarely, partial hepatectomy is necessary.

There are many drugs which cause liver injury Labetalol, Troglitazone, Methyltestosterone, Oxandrolone, Stanozol, Fluoxymesterone, Danazol, Oxytetracycline, Tetracycline, Griseofulvin, Terbinafine, Interferon, Zidovudine, Naltrexone, Chlorambucil, Sterptozocin, Dacarbazine, Thioguanine, Etoposide, Azathiopurine, Alprazolam, Brotizolam, Chlordiazepoxide, Clobazam, Clorazepam, Demoxepam, Diazepam, Estazolam, Flumazenil, Flurazepam, Halazepam, Prazepam, Quazepam, Temazepam, Triazolom, Chloral hydrate, Aspirin, Sodium Salicylate, Choline magnesium trisalicylate, Salsalate, Diflunisal, Sulfasalazine, Osalazine, Acetaminophen, Bromfenac, Captopril, Enalapril, Enalaprilat, Lisiopril, Benazepril, Fosionopril, Trandolapril, Quinapril, Ramipril Moexipril, Perindopril.

Conclusion

There are many drugs which cause hepatotoxicities. The drug are used for their theraputic action but some of them cause hepatotoxicities. The hepatotoxicities are more general when the drugs in this project are used in combinations. The drug when given to any hepatic disorder patient, the drug give hepatotoxicities. The liver function tests must be run on the patients who are having hepatic dysfunction & taking the treatment of such drugs described in this project. The injury in such patients must be checked time to time. If the injury increases, such drugs must be stopped they may become fetal to the patients. The drugs like anticancers & antituberculers are very dangerous for the liver dysfunction patients. Some drugs cause minor type of hepatotoxicity & they don't create severe problems, so they can be used further. The dose of hepatotoxic drugs must be maintained for individual. Mostly drugs are metabolised & detoxified by liver, so mostly drugs cause hepatotoxicity.

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Conflict of Interest

None.

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