

Drug Induced Hepatic Steatosis - A Review

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Abstract: Hepatic steatosis is the abnormal retention of lipid within the hepatocytes in the form of vesicles. The vesicles can be micro vesicular or macro vesicular. Various factors such as metabolic, nutritional, alcoholic and drugs can induce hepatic steatosis. Drugs such as Amiodarone, methotrexate, diltiazem, expired tetracycline, HAART, tamoxifen, etc. can induce hepatic steatosis over a period of time. Drug induced hepatic steatosis will remain a problem that carries both clinical and regulatory significance as long as new drugs come into the market.

Keywords: Liver, Steatosis, microvascular, steatosis, macrovascular steatosis

Introduction

The liver plays a major role in drug metabolism. Therefore, it is vulnerable to wide spectrum of liver diseases. It has been reported that more than 900 drugs have been identified to cause liver injury including hepatic inflammation, necrosis, steatosis, fibrosis, apoptosis and hepatocellular carcinoma (1). Hepatic steatosis is commonly known as fatty liver diseases and occurs due to the abnormal accumulation of lipids within the hepatocytes in the form of vesicles. The vesicles can be macrovascular or micro vascular (25). These micro and macrovascular vesicles are associated with acute hepatic steatosis and chronic steatohepatitis respectively. Microvascular hepatic steatosis is characterised by the presence of numerous small lipid droplets around the cytoplasm without peripheral displacement of nucleus (13). The drugs associated with microvascular hepatic steatosis are Valproic acid and anti inflammatory drugs (16), anti retroviral drugs (17). Macrovascular steatosis is characterised by the presence of small to large lipid droplets in the cytoplasm of the hepatocyte, with displaced nucleus (12 -14). Macrovascular steatosis is often associated with glucocorticoids, methotrexate and amiodarone (15).

Hepatic steatosis can occur due to various factors like metabolic, nutritional, alcoholic and drugs. Various classes of drugs such as antiarrhythmic (2), anticancer, anti-retroviral, anti-inflammatory, antiepileptic, antihypertensive drugs have been found to cause fatty infiltration (25). During the biotransformation of various drugs, the liver produced active metabolites which are directly implicated in disrupting the fatty-acid oxidation within the mitochondria of the hepatocytes. The vesicles eventually break open which elicits an inflammatory response. If left untreated, the fatty infiltration causes necrosis and apoptosis through lipid peroxidation (25).

Drugs that induce hepatic steatosis can be classified into three groups: The first group includes the drugs that share a characterised mechanism of hepatotoxicity (Amiodarone, perhexiline maleate, diethylaminoethoxyhexestrol). The second group includes drugs which can precipitate latent form of NASH (Tamoxifen, an adjuvant used in breast cancer) (19). The third group drugs involve that induce sporadic cases of steatosis without any pathological evidence of mechanism of liver injury (20). The occurrence of drug-induced liver disease is higher than the reported range of 1 in 10000 to 1 in 100000 (18). Chronic administration of anti-tubercular, anti-retroviral, immunosuppressive drugs is reported to induce free radical generation during their biotransformation in the liver. Further, these reactive intermediates is said to interfere with fatty oxidation and induce cytokines, several inflammatory markers during the progression of chronic liver diseases. In the present review we summarize some important classes of drugs that are responsible for hepatic steatosis.

Amiodarone

Amiodarone is a diiodinated benzofuran derivative; class 111 antiarrhythmic drugs and is highly effective drug used for the treatment of atrial and ventricular arrhythmias. The principal metabolite is desethylamiodarone. (3). This drug causes thyroid, pulmonary toxicities, optic neuropathy, and peripheral neuropathy. Among which hepatotoxicity is predominate. During the course of amiodarone, hepatic toxicity occurs through i.v. infusion and this causes dysfunction of liver enzymes within 2-3 days of administration. Chronic oral therapy of amiodarone treatment increased serum aminotransferase up to 3 fold than the normal levels. The drug inhibits enzyme complexes in electron transport chain, impairs β -oxidation and uncouples oxidative phosphorylation in the mitochondria of the liver (4). It has been reported that asymptomatic elevation of serum transaminases were observed in 4-80% of patients treated with amiodarone (21). Symptomatic hepatotoxicity is seen in 1- 3% of the population treated with amiodarone (4).

Tamoxifen

It is a selective estrogen receptor modulator. It is used as an adjuvant for breast cancer. Tamoxifen causes mild to moderate steatohepatitis, macrovascular steatosis and rarely cirrhosis. The factors such as glucose intolerance and diabetes, obesity, hyperlipidemia and hypertension are directly implicated with tamoxifen induced liver injury (5). The drug accumulates in the mitochondria resulting in impaired β -oxidation and respiration by inhibiting carnitine palmitoyltransferase 1, the rate-limiting enzyme. This drug also inhibits topoisomerases thus depleting mitochondrial DNA and suggested that decrease fat removal from the liver, thus causing hepatic steatosis despite a secondary down-regulation of hepatic fatty acid synthase expression. (6). It has

been observed that tamoxifen causes steatohepatitis in significant percentage of cancer patients with pre-existing liver steatosis. This is especially high in patients with high BMIs and high glucose levels (26).

Methotrexate

Methotrexate is an antimetabolite and antifolate drugs. It is commonly used for the treatment of cancer, autoimmune diseases and ectopic pregnancy (25). Methotrexate interferes with folate metabolism by inhibiting dihydrofolate reductase enzyme thereby interfering with the purine and pyrimidine metabolism decreasing DNA and RNA synthesis. Methotrexate-induced liver dysfunction usually occurs with chronic use in inflammatory diseases. The underlying mechanism has not been fully understood. However, oxidative stress leading to increased production of ROS and decreased defense mechanism has been implicated to the cause of hepatic steatosis (11).

Valproic acid

Valproic acid is a broad spectrum antiepileptic drug with wide range of adverse effects. Long term use of this drug gives rise to insulin resistance, weight gain and lipid abnormalities (7). It produces hepatic steatosis by bioactivation. The mitochondrial enzymes in liver, cytochrome P450 converts valproate to 4-valproic acid. This acid acts as a potent inducer of micro vascular fat accumulation (9). About 61% of the patients treated with valproic acid were found to develop hepatic steatosis based on ultrasound imaging (8).

Antiretroviral Drugs

All three classes of antiretroviral drugs, nucleoside/ nucleotide analog reverse transcriptase inhibitors, protease inhibitors and non-nucleoside analog reverse transcriptase inhibitors are known to cause any one kind of chronic liver injury (10), (27). Studies have shown that the risk of hepatotoxicity is significantly higher in patients with viral hepatitis. Mitochondrial toxicity is the major form of liver injury in HIV patients. This is because of the presence of nucleotide reverse transcriptase inhibitors that can inhibit mitochondrial polymerase enzyme which results in depletion of mitochondrial DNA, lactic acidosis and microvesicular steatosis (11), (27).

Chemotherapy

Drugs including 5-FU, platinum derivatives and taxanes in chemotherapy cause oxidative stress in cancer cells and normal cells leading to hepatic steatosis (21). Therapeutic agents like L- asparaginase, mitomycin C, dactinomycin, bleomycin sulphate are known to be linked with fatty liver. (22). 5- Fluorouracil, a flouropyrimidine antimetabolite causes irreversible inhibition of thymidylate synthase. About 35-47% of patients receiving 5-FU are found to have fatty liver (23-24).

Conclusion

Hepatic steatosis is a rare condition. The environmental and Genetic factors also play a major role to why a rare patient will develop idiosyncratic hepatotoxicity. Understanding the molecular mechanism involved and the associated risk factors, may offer better clues in identifying the patients susceptible to this type of injury. It is also necessary to understand and study each drug thoroughly during the clinical trials before marketing it since the adverse effects can be seen only after a very long period.

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