

Drug Induced Liver Injury

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Abstract: A large number of chemical agents used for diagnostic and therapeutic purposes can produce varying types of hepatic injury by different mechanisms. Drug induced liver injury accounts for 3-9% of all adverse drug reactions. Various drugs that have been implicated in causing liver injury include non steroidal antiinflammatory drugs (NSAIDs), antituberculous agents, nucleoside reverse transcriptase inhibitors, non nucleoside reverse transcriptase inhibitors, protease inhibitors, penicillins, cephalosporins, tetracyclines, macrolides, sulfonamides and trimethoprim, antifungal agents, antidepressants, antipsychotics, anticonvulsants, anti-anxiety drugs, acetylcholinesterase inhibitors, alcohol, cocaine, ecstasy, antihypertensive agents, oral hypoglycemics, and a few others like statins, estrogens, halothane, amiodarone, methotrexate, nitrofurantoin, disulfiram, omeprazole, D-Penicillamine, and heparin. This review focuses on the different types of drug induced liver injuries, their mechanisms, and the individual drugs causing liver injury.

Introduction

A large number of chemical agents used for diagnostic and therapeutic purposes can produce varying types of hepatic injury by different mechanisms. More than 600 agents are known to cause hepatic injury¹. The incidence of drug induced liver injury has been increasing perhaps due to a large number of new compounds introduced into clinical use. Drug induced liver injury manifests most commonly as acute toxicity. It accounts for 3-9% of all adverse drug reactions².

Drugs Causing Liver Injury (Table 1)

Anti-inflammatory (Analgesic Agents)

Non Steroidal Antiinflammatory Drugs (NSAIDs) : The NSAIDs are widely used as analgesics and antipyretics, both as prescription drugs and over the counter purchases. Although the risk of clinically apparent liver injury is low (1-8 cases per 100,000 patient years of NSAID use), it can be serious and can create confusion in diagnosis. Hepatic injury is considered a class effect of NSAIDs by USFDA. An idiosyncratic reaction (immunologic or metabolic) is generally implicated in NSAID induced liver injury.

Salicylates : Salicylates have been documented to cause dose-

dependent liver injuries since the 1970's. Aspirin generally causes an acute, mild, and reversible form of hepatic injury. Aminotransferase values are elevated in the mild to moderate range with AST levels somewhat higher than ALT levels³. Severe hepatic injury with aspirin is reported in only 3% of the cases with patients presenting with encephalopathy, coagulopathy, and death. Serum levels of 15mg/ml or greater cause hepatic injury although lower levels have also been reported⁴. Susceptibility to aspirin induced hepatotoxicity is seen in patients with juvenile rheumatoid arthritis, systemic lupus, rheumatic fever, and preexisting liver disease. The mechanism of aspirin induced liver injury is thought to be the accumulation of toxic metabolites. The association between aspirin and Reye's syndrome has been widely reported⁵. This syndrome is characterized by severe hepatic damage and encephalopathy occurring in children and usually preceded by a respiratory viral disease or varicella.

Acetaminophen : Acetaminophen is well tolerated at the usual therapeutic doses. However, it is the leading cause of liver failure when used in intentional overdoses. A fatal dose is estimated to be 10-15g. The histological picture is one of hepatocellular necrosis with serum ALT and AST levels markedly elevated at presentation (>3000IU/L)⁶. During the first 1-2 days, nausea, vomiting, and abdominal pain occur. The symptoms subside in the next 24 hrs and the third phase of injury develops after 48 hrs when signs of hepatic damage and associated cardiotoxicity and renal failure develop. An unstable quinone metabolite, N-acetyl-p-benzoquinone imine is the toxic moiety responsible and early treatment with N-acetyl cysteine is generally effective.

Diclofenac : Diclofenac has been implicated in over 200 instances of hepatocellular injury with several fatalities⁷. Anorexia, nausea, and malaise are the early symptoms with fever and rash occurring in 25% of the patients. Acute injury generally resembles acute viral hepatitis. The prognosis is usually good although rare cases of fulminant hepatic failure have been reported with diclofenac.

Antimicrobial Agents

Antimicrobial agents have been associated with different forms of hepatotoxicity ranging from minor abnormalities in liver function tests to fulminant hepatic failure. The reactions are generally

Table 1 : Drugs causing acute hepatocellular injury.

NSAIDs/Analgesics	
Acetaminophen	
Oxaprozin	
Diclofenac	
Piroxicam	
Etodolac	
Phenylbutazone	
Antimicrobials	Anticonvulsants
Sulfonamides	Phenytoin
Erythromycin	Carbamazepine
Isoniazid	Valproic acid
Rifampicin	
Pyrazinamide	
Tetracycline	Miscellaneous
Paraaminosalicylic acid	Anabolic and contraceptive steroids
	Disulfiram; Troglitazone; Nefazodone;
	Flutamide; Propylthiouracil

Table 2 : Drugs causing chronic liver injury.

Chronic Hepatitis	Chronic Cholestasis
Isoniazid	Antibiotics
Isoniazid	Ampicillin
Methyldopa	Tetracycline
Sulfonamides	Cotrimoxazole
Nitrofurantoin	Erythromycin
Dantrolene	Clindamycin
Propylthiouracil	
Ethanol	Antipsychotics
Methotrexate	Chlorpromazine
Amiodarone	Haloperidol
Tolbutamide	
Oral contraceptives	Miscellaneous
Thioguanine	Tolbutamide
Organic arsenicals	Terbinafine
	Cimetidine
	Azathiopurine
	Ticlopidine
	Ibuprofen

unpredictable and idiosyncratic and the injury is usually self-limiting once the offending agent is withdrawn.

Antituberculous Therapy

Antitubercular drugs frequently cause liver injury with significant liver enzyme elevations in 20% of those treated⁸.

Isoniazid : Isoniazid causes serious hepatic injury (acute hepatocellular necrosis) resembling acute viral hepatitis in upto 1% of patients⁹. Susceptibility to isoniazid induced hepatotoxicity is enhanced in pregnancy, older subjects, and in those with hepatitis B infection. Fast acetylators are more prone to developing hepatotoxicity.

Rifampin : Rifampin rarely causes hepatotoxicity when used alone. The use of rifampin in combination with isoniazid is more hepatotoxic because rifampin enhances the production of the toxic metabolite, acetylhydrazine.

Pyrazinamide : Pyrazinamide based antitubercular regimens have been associated with a higher frequency as well as a more severe pattern of liver injury than those without it.

Antiviral Agents

Antiretrovirals have been associated with hepatic injury of varying patterns. About 5-15% of all patients receiving highly active antiretroviral therapy (HAART) develop elevations in liver enzymes¹⁰.

Nucleoside reverse transcriptase inhibitors (NRTI's) : NRTI's have occasionally led to episodes of acute hepatitis and steatohepatitis. Zidovudine is the NRTI that is most commonly associated with hepatocellular injury¹¹. Didanosine in high doses has been associated with hepatocellular injury and fulminant hepatic failure.

Non Nucleoside reverse transcriptase inhibitors (NNRTI's) : Hepatotoxicity with NNRTI's is seen in about 10% of cases¹². Nevirapin has been associated with a number of clinical hepatic events when used for postexposure prophylaxis in non-HIV infected patients.

Protease Inhibitors : Among the protease inhibitors, ritonavir carries the highest risk of hepatotoxicity. Indinavir and atazanavir cause a benign increase in unconjugated bilirubin in HIV infected

patients.

Beta Lactams

Penicillins : Natural penicillins rarely produce liver injury. However, semisynthetic penicillins are responsible for a wide range of hepatotoxic reactions. Cholestatic hepatitis has been associated with oxacillin, cloxacillin, dicloxacillin, and flucloxacillin. Amoxicillin in combination with the beta lactamase inhibitor clavulanic acid, is associated with significantly increased hepatotoxicity, the incidence being one in every 80,000 - 90,000 prescriptions¹³. Clinical manifestations such as nausea, vomiting, fatigue, malaise, abdominal pain, fever, jaundice, and pruritus generally occur within four weeks of starting treatment and recovery usually occurs within 1-8 weeks.

Cephalosporins : Cephalosporins are closely related to penicillins and show cross reactivity with them. Hepatotoxicity with cephalosporins has been rarely reported. However, moderate elevations of plasma aminotransferase levels are known to occur with all cephalosporins and are seen in about 6% patients with the 3rd generations agents¹⁴.

Tetracyclines : Oral tetracyclines are rarely associated with hepatic injury. The intravenous form, which was in use previously, produced a syndrome resembling acute fatty liver of pregnancy. Minocycline has been reported to cause an early onset, hypersensitivity reaction associated with hepatitis and eosinophilia as well as a delayed onset chronic hepatitis presenting as a systemic lupus erythematosus like syndrome.

Macrolides : Hepatotoxicity with macrolides has been known since the 1960's when cholestasis was first reported with erythromycin estolate. It has been seen that all erythromycin esters can produce cholestasis with jaundice and pruritus occurring within 3 weeks of exposure. Recovery is usually complete and fatal hepatitis doesn't occur¹. Although the hepatotoxic potential of newer macrolides is low, reports of cholestasis have been there with azithromycin, clarithromycin, and roxithromycin¹⁵.

Sulfonamides and trimethoprim : Sulfonamides have been known to produce a wide spectrum of liver injuries including acute hepatocellular injury, granulomas, as well as cholestasis¹⁶. Immunoallergy is the mechanism responsible and the patients present with rash, fever, and eosinophilia. Fatal liver injury is reported with sulfasalazine, usually within 8 weeks of starting therapy. Cotrimoxazole (Trimethoprim sulfamethoxazole) characteristically produces a cholestatic or mixed pattern that can progress to fulminant liver failure. Dapsone therapy produces a sulfone syndrome with fever, rash, jaundice, and anemia.

Antifungal Agents

Azole antifungals : The most common antifungal agent associated with hepatic injury is ketoconazole with severe liver injury seen in 1 in 15,000 recipients¹⁷. Fluconazole and itraconazole are less frequently associated with hepatitis.

Table 3 : Drugs causing hepatic granulomas.

Quinidine	Sulfonamides
Hydralazine	Penicillin
Allopurinol	Methyldopa
Halothane	Gold
Phenylbutazone	

Terbinafine : Terbinafine produces hepatocellular and cholestatic injury in 1 in 50,000 persons¹⁸ usually 4-6 weeks after initiation of therapy.

Other antifungal agents : Lipid formulations of amphotericin B have been associated with hepatic necrosis. Flucytosine has been associated with hepatotoxicity when used in combination with other antifungals.

Antidepressants

Older antidepressants such as monoamine oxidase inhibitors have been associated with liver injury. MAO inhibitors are derivatives of hydrazine and are potential hepatotoxins. Iproniazid led to overt hepatitis in 1% with case fatalities approaching 20%¹⁹ following which it was withdrawn. Tricyclic antidepressants produce predominantly cholestatic liver injury. Usage of noncyclic antidepressants such as nefazodone has led to episodes of acute liver failure with symptoms occurring 7-28 weeks after treatment. Trazodone also has been implicated in cases of acute cholestatic liver injury as well as chronic active hepatitis and the period of onset of symptoms has been as long as 18 months. The selective serotonin reuptake inhibitors (SSRI's) are one of the most commonly used antidepressants and around 0.5% of long term recipients of fluoxetine show asymptomatic mild elevation in liver enzymes. Cases of acute hepatitis and cholestatic jaundice have also been reported with fluoxetine usage²⁰.

Antipsychotics

Many antipsychotics are associated with liver injury. Cholestatic jaundice is an important side effect with chlorpromazine and occurs within the first month of therapy. There is around 8-10 fold elevation of liver alkaline phosphatase and aminotransferases²¹. Manifestations of hypersensitivity like fever and eosinophilia can occur in 70% of patients. Recovery of liver function from jaundice occurs within 2-8 weeks of stoppage of drug but protracted cholestasis has been seen in few affected individuals. Haloperidol usage in some cases is also associated with cholestasis. Newer drugs such as clozapine and risperidone are known to cause hepatocellular injury, while acute hepatitis has been seen with olanzapine.

Anticonvulsants

Many antiepileptic drugs are known to cause liver injury. Drugs such as phenytoin, carbamazepine, and phenobarbitone are known to cause a type of antiepileptic hypersensitivity syndrome. Frequency of occurrence of this syndrome is approximately 1 in 3000 exposures and the onset of syndrome is within the first 2-8 weeks after starting the treatment. The syndrome is characterized by a triad of fever, skin rash and involvement of internal organs such as liver, kidney, and bone marrow. The syndrome is reversible but in certain cases despite the discontinuation of the offending drug, the syndrome might progress and may be fatal. Valproic acid usage especially in the paediatric age group has been associated with hepatocellular injury. The onset of injury is within 4-16 weeks of treatment with mild to moderate elevations of ALT and AST values. Anorexia, nausea, vomiting, and somnolence are common symptoms of valproic acid hepatotoxicity. Fatal hepatotoxicity is seen in around 1% of patients. Use of lamotrigine is also associated with incidence of acute hepatitis, the onset of

Table 4 : Drugs causing hepatic neoplasms.

Adenoma	Danazol, contraceptive and anabolic steroids
Hepatocellular Carcinoma	Thorium dioxide (Thorotrast), contraceptive and anabolic steroids
Cholangiocarcinoma	Thorium dioxide (Thorotrast)
Angiosarcoma	Vinyl chloride, Thorium dioxide, inorganic arsenicals

which occurs between 2 and 3 weeks²². Histologically, it presents as acute hepatic necrosis or focal hepatitis with mild portal inflammation. Serious hepatotoxicity has been reported with the use of felbamate²³. The period of onset of injury is between 1-7 months of starting therapy. A reactive metabolite atropaldehyde is seen to be responsible for causing liver injury.

Anti-anxiety Drugs

Benzodiazepines, such as chlordiazepoxide, diazepam, and flurazepam, have very low hepatotoxic potential, with only a few case reports demonstrating a cholestatic pattern of injury²⁴.

Acetylcholinesterase inhibitors

Tacrine is a reversible cholinesterase inhibitor used for Alzheimer's disease. The ALT levels exceed upper limit of normal in upto 50% of recipients in the first 12 weeks of tacrine therapy. tacrine is metabolized by CYP1A2 to reactive metabolites that may cause hepatotoxicity.

Drugs of abuse

Alcohol : Ethanol produces a variety of dose related deleterious effects in the liver. The primary effects are fatty infiltration of the liver, hepatitis, and cirrhosis. The accumulation of fat results from both inhibition of the tricarboxylic acid cycle and the oxidation of fat. Chronic inflammation and necrosis lead to fibrosis, and subsequently cirrhosis of the liver. the histologic hallmark of cirrhosis is the formation of 'Mallory bodies' related to an altered intermediate cytoskeleton.

Cocaine : Cocaine causes dose-related hepatotoxicity. Although cocaine induces oxidative stress in hepatocytes, its mechanism is controversial. Cocaine hepatotoxicity has been well characterized in mice. Its occurrence in humans is very rare.

Ecstasy (3, 4-methylenedioxymethamphetamine MDMA) : There have been a number of case reports of severe acute hepatotoxicity in response to MDMA with a latent period of days to weeks. An immune mechanism is postulated with tissue eosinophilia seen in some cases.

Antihypertensive Agents

Methyldopa : Methyldopa is a well known cause of liver injury. this develops within first 3 months of therapy in 90% patients and usually resolves when the drug is discontinued.

ACE inhibitors and Angiotensin II receptor blockers : ACE inhibitors (captopril, enalapril, fosinopril) usually cause bland cholestasis or cholestatic hepatitis. Fulminant hepatic failure has been reported with enalapril and lisinopril²⁵. Among the Angiotensin II receptor blockers, liver toxicity has been observed with losartan, irbesartan, and candesartan. However, long term follow-up data

with these are still unavailable.

Calcium channel blockers (CCB's) : Only few reports of CCB related liver injury are available. Diltiazem has been associated with granulomatous hepatitis whereas nifedipine has caused lesions containing Mallory bodies¹. Mild elevations in aminotransferase levels are reported with amiodarone. Chronic injury, including an alcohol-like illness, is also seen with amiodarone as a consequence of its long half life.

Oral Hypoglycemics

Sulphonylureas : The prototype sulphonylureas including acetohexamide, methohexamide, carbuthamide, and glibuthiazole have been withdrawn because of severe hepatotoxicity². Hepatic injuries with chlorpropamide, tolbutamide, and tolazamide have been reported occasionally. Cholestatic jaundice is seen with sulphonylureas in 1% of recipients²⁶.

Thiazolidinediones : Troglitazone, a peroxisome proliferator activated receptor gamma agonist, was withdrawn after it caused over 100 cases of hepatotoxicity²⁷. Patients with troglitazone hepatotoxicity presented with nausea, vomiting, and jaundice after an average of 4 months. There have been two reports of hepatotoxicity with rosiglitazone²⁸ and one report of reversible acute hepatocellular injury with pioglitazone²⁹. FDA recommends liver function tests at baseline and every two months thereafter during first year of treatment with thiazolidinediones. The drug is to be discontinued if ALT levels remain persistently elevated (>3ULN).

Others : There have been two reports of acute cholestatic hepatitis with metformin whereas several reports of hepatotoxicity are available with acarbose²².

Lipid lowering agents

Mild transient elevations in ALT and AST levels have been reported with most lipid lowering drugs. Statins produce liver test abnormalities in < 5% of patients. Frequency of acute liver failure is low with statins (0.2 per 100,000 patients)³⁰, with cholestatic injury predominating. Autoimmune hepatitis has been seen with fenofibrate. Dose related hepatotoxicity is also seen with nicotinic acid.

Hormones

Jaundice with oral contraceptives, albeit rare, is usually seen in the first month of therapy. The incidence of hepatic adenomas with long term oral contraceptive use is about 3.4 per 100,000¹⁰. Tamoxifen has been known to cause cholestasis, hepatocellular carcinoma, acute hepatitis, steatosis, and steatohepatitis. The incidence of hepatic steatosis is approximately 30% with tamoxifen and 10% with toremifene, an analog of tamoxifen³¹. Anabolic steroids having an alkyl group at the C-17 position are hepatotoxic. Jaundice is seen with high doses of androgens often accompanied by malaise, pruritus, and anorexia. Hepatic adenomas and carcinomas are also seen to occur with androgens. Among the antiandrogens, flutamide causes hepatotoxicity in 1-5% subjects. Danazol and cyproterone acetate have led to elevations in plasma aminotransferase levels to the extent of 30-50%.

Anesthetics

Halothane can produce fulminant hepatic necrosis at approximately

1 in 10,000-35,000 exposures¹. Patients present with fever, nausea, anorexia, and vomiting accompanied by a rash and peripheral eosinophilia. The mechanism behind halothane hepatitis is thought to be an immune response to trifluoroacetylated proteins on hepatocytes.

Miscellaneous Agents

Amiodarone : Amiodarone causes abnormal liver tests in 15-80% patients whereas clinically significant disease occurs in 0.6-3%. It is the drug most commonly implicated in steatohepatitis³². Amiodarone induced steatohepatitis occurs after exposure to the drug for long durations, the mean being 21 months. Patients present with fatigue, nausea, vomiting, malaise, and weight loss.

Methotrexate : Prolonged treatment with methotrexate can lead to hepatic fibrosis and cirrhosis. Risk factors include alcohol ingestion, obesity, diabetes, and underlying liver disease.

Nitrofurantoin : Nitrofurantoin produces diverse patterns of hepatotoxicity including acute hepatocellular, mixed, cholestatic, and granulomatous reactions. A chronic active hepatitis reaction with nitrofurantoin is common in elderly women exposed for longer than six months. This may progress to cirrhosis and hepatic failure.

Disulfiram : Disulfiram causes hepatic abnormalities in 25% of patients who present with nausea, fatigue, malaise, and occasionally jaundice 2-8 weeks after starting the drug.

D-penicillamine : Many cases of cholestatic jaundice with d-penicillin have been reported within the first 2-4 weeks of initiating therapy³³.

Heparin : Abnormalities of liver function tests occur frequently in patients receiving heparin either subcutaneously or intravenously. Mild elevations of the activities of hepatic transaminases in plasma occur without an increase in bilirubin levels or alkaline phosphatase activity.

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