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Mechanism of Action of Hepatotoxicity Drugs

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Abstract: ***Liver is the largest gland functioning as storage, manufacturing and biotransformation process. Due to increase exposure of drugs like anti-tubercular, anti-convulsants, NSAIDS, antibiotics etc., causes liver damage like elevation in serum transamines, depletion of glutathione level, oxidative stress, formation of reactive metabolites by cytochrome p450 enzyme , depletion of adenosine triphosphate level, hypersensitivity reactions , sometimes the cause is not known (idiosyncratic toxicity) and hence many scientist and researchers have reported hepatoprotectants drugs.***

Keywords: biotransformation, mechanism of hepatotoxicity drugs, hepatoprotectants drugs

1. Introduction

Liver is a largest gland in human body, situated in right side of upper abdominal cavity. Hepatocytes play vitals function such as production of bile, metabolism of fats, carbohydrates and protein, enzymes activation, storage of glycogen, vitamins, and minerals, synthesis of plasma proteins such as albumin and clotting factors etc. The main function is drug metabolism and excretion. here biotransformation of drugs occurs generally biotransformation process involves 2 phases

Phase-1 – conversation of parent drug to polar metabolites, here oxidation, reduction, hydrolysis. It mainly involving of p450 enzymes

Phase-2 – endogenous substrate forms a polar conjugate, here glucuronidation, acetylation, conjugation, sulfation, methylation, water conjugate. Theyare catalysed by glutathione-s-transferase, UDP-glucuronosyl transferase and n-acetyl transferase.

2. Mechanism

In liver generally metabolism of drug there is breakdown of lipophilic compound to watersoluble substance and then it excreated out of the body. Sometimes during this biotransformation of drugs it leads formation of reactive metabolite, these metabolite bind to nucleic acids, cellular protein and lipids and then it lead to DNA damage, loss of protein function and lipid peroxidation

Sometimes due to formation of reactive metabolites there is activation adaptive immune response, in liver the Kupffer cells and natural killer Tcells which protect from viral and bacterial toxins and also xenobiotics due to activation of immune system and then lead to stress in endoplasmic reticulum and mitochondria some drugs activates these immune cells and forms proinflammatory mediators such TNFalpha, interferone beta and gamma.

Some drugs also causes hypersensitivity reactions such as skinrash, fever, eosinophila due todetection of antibodies against hepatic proteins

Due to alteration in DNA expression which to genetic polymorphism it inhibit the membrane transporters of drugs and finally drug resistance association occurs and therefore increase in bilirubilin level. Some drugs also alter activity biliary transporter bile salt excretory pump which lead to cholestasis.

Normally liver mitochondria are essential in hepatocyte survival as mediator for apoptosis and necrosis. Some dugs causes mitochondria injury due to activation of c-jun-N-terminal kinase(JNK) which is death pathway. Eg: acetaminophen.

Glutathione (natural detoxifier) shows antioxidant effect which is produce in mitochrondria plays important roles in cellular defence, it improve protein, enzyme and bilirubin levels. But due depletion of this glutathione level it leads increase in serum liver enzymes such ALT, ALP, and alkaline phosphates than the normal limit also cause liver damage.

Some drugs cause disruption of calcium homeostasis which causes depletion of adenosine triphosphate levels and finally leads cell rupture and cell breakdown.

Heptotoxicity Drugs

Drug	*Mechanism of Action*	*Long Term Usage*
ANTIBIOTICS Amoxicillin/clavulanate Trimethoprim/sulfamethoxazole Fluroquinolones Macrolides Minocycline Nitrofurantoin Clarithromycin	These drugs mainly increases toxic metabolites by cytochrome p450 enzymes	Chronic hepatic injury Fulminant hepatitis Granuloma in liver Microvesicular steatosis Vanishing bile duct syndrome
ANTIEPILEPTICS Phenytoin	These drugs mainly increases transaminase enzymes(aminotransferase, lactic dehydrogenase,	Acute hepatic injury Cholestasis

Carbamazepine Lamotrigine	alkaline phosphate, bilirubin, prothrombine)	Granuloma in liver Vanishing bile duct syndrome Liver cell necrosis
ANTI TUBERCULAR Rifampicin Isoniazid Pyrazinamide	These drugs shows asymptomatic transaminase elevations and also forms toxic metabolites by cytochrome p450 enzymes in liver microsomes	Acute hepatic injury Chronic hepatic injury Granuloma in liver Fulminant hepatitis
NSAIDS Acetaminophen Diclofenac Ibuprofen Naproxen	These drugs shows elevations of serum transamines and alkaline phosphate , and also depletion of glutathione level and lipid peroxidation	Acute hepatic injury Granuloma in liver Necrosis of cetrilobular hepatocytes
HYPERLIPIDEMIC DRUGS Statins Niacin Fibrates	These drugs mainly impairment of bile acid transport protein, reactive metabolite of p450 enzymes.	Cholestasis
ANAESTHETIC AGENTS Halothane Chloroform Isoflurane Enflurane Desflurane Nitrous oxide	These drugs mainly forms reactive metabolite by cytochrome p450 enzymes and later free radical generation occurs.	Hepatic centrilobular necrosis
IMMUNOSUPPRESSIVE Gold salt Azathioprine Methotrexate Infliximab Azathioprine /6-mercaptopurine	These drugs cause transaminase elevations , some cases increase methyltransferase which leads to hypermethylation	Macrovesicular steatosis
ANTI CONVULSANTS Valproic acid	These drugs act on mitochondrial coenzyme depletion which involves in beta-oxidation of fat in body	Acute hepatic injury Microvesicular steatosis
ANTI PSYCHOTIC DRUGS Chlorpromazine	These drugs inhibits beta-oxidation of fat, reactive metabolite of p450 enzyme and asymptomatic mild transient reversible elevations of liver enzymes	Heptocellulatr cholestasis Microvesicular steatosis
ANTI THYROID DRUGS Propylthiouracil Methimazole	These drugs cause increase of transaminase , alanine aminotransferase, asparate aminotransferase, alkaline phosphate, gamma glutamyltransferase.	Cholestatic heptasis Cytotoxic hepatasis
Corticosteroids/ Glucocorticoids and Anabolic Androgenic Drugs	Generally these glucocorticoids promote glycogen storage in liver , but due this agents steatosis is observed in adults and children	Steatosis Non alcoholic fatty liver
ANTI HYPERTENSIVES Hydralazine Metaprolol	These drugs cause asymptomatic increase of serum transaminase , and they also convalently inhibits glutathione, ascorbic acid, superoxidedismutas, therefore release free radicals	Acute hepatic injury Microvesicular steatosis Granuloma in liver Cholestasis
ANTI FUNGAL DRUGS Ketoconazole	This drugs decreases glutathione and also convalently bind to hepatic proteins in microsomes and also increase of serum transaminases	Acute cholestasis
ANTI COAGULANTS Heparin	These drugs increase serum transaminase which leads to the damage of hepatocytes by reactive metabolites by p450 enzymes , decrease of adenosine triphosphate.	Acute liver injury Massive hepatocellular necrosis Cholestasis
PLATELET INHIBITOR Ticlopidine	These drugs cause detoxification of glutathione s transferase enzyme and also forms CYP2C9 reactive metabolite which convalently binds to macromolecules and forms free radicals	Hepatic fibrosis Chronic hepatic injury
ANTI NEOPLASTIC Thioguanine Cyproterone Tamoxifen Imatinib	These drugs directly cause hepatic toxicity due releasing of toxic metabolite.	Nodular regenerative hyperplasia Hepatic vascular injury Veno occlusive disease
ANTI MALARIAL DRUGS Amodiaquine	These drugs forms a reactive metabolite iminoquione by peroxide and microsomes and then lead to reversible bind to proteins and finally cell function decreases	Acute hepatic injury Jaundice
MUSCLE RELAXANT Chlorzoxazone Dantrolene	These drugs causes increase in transaminases	Acute cholestasis

ANTI RETROVIRAL DRUGS Ritonavir Indinavir nelfinavir lamivudine tenofovir zidovudine didanosine nevirapine efavirenz	These drugs due to decrease mitochondria activity , direct toxicity of liver, hypersensitivity reactions which leads increase of liver enzymes	Microvesicular steatosis Acute fatty liver

Pharmacotherapy of hepatotoxicity

- Reduces the dose of medications
- Life style modifications such as limit alcohol,losing weight,careful monitoring of liver function.
- IV administration of carnitine (which enhances beta oxidation of fat)
- Diuretics -for fluid accumulation
- Nutrient supplementation - taurine, arginine, polyenylphosphatidylcholine, alphalipoic acid, vitamin-B, antioxidant vitamins (ADE), methylsulfonylmethane , s-adenosyl methionine, methionine.
- Hepatoprotective drugs – silymarin, membrane stability drugs, anti-lipid peroxidative, anti-oxidative, anti-inflammatory, immune modulative drugs.
- Glycyrrhiza glabra, picrohiza kurro, Phyllanthus amarus shows good hepatoprotective effect.

3. Conclusion

Normally liver is the primary biotransforming organ, because all the drugs are metabolised and excreted (detoxification). It is also potentially vulnerable to the toxic action of xenobiotic substances but too much of medication intake the liver damage occur. So to control liver damage hepatoprotectants drugs are prescribed but idiosyncratic cause liver transplantation occurs. This hepatoprotectants shows antioxidative effect and reduces the severity of liver damage.

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