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Review Article

AN OVERVIEW ON DRUG-INDUCED HEPATOTOXICITY

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ABSTRACT

Liver is a vital organ, contributing in most of the metabolic and physiological processes of our body. It plays principal role in detoxification of various drugs and xenobiotics. Though liver possess tremendous regenerative capacity, but metabolism of various chemicals severely damage the hepatic system. Drug induced hepatotoxicity (DIHT) is a major concern in this respect. The drugs we consume to treat various diseases, very often, their metabolic intermediates cause liver toxicity. The lion's share of the idiosyncratic drug reactions ultimately results either in liver transplantation or even death. DIHT is a major medical concern at present and several drugs have been withdrawn from the market due to their hepatotoxic phenotype. Therefore, considering the phenomenon of DIHT, we have documented various aspects of DIHT, also discussing about the mode of toxicity of the drugs.

Keywords: Drug-induced hepatotoxicity, Hepatoprotective, Hepatotoxicity, Idiosyncratic drug reactions, Liver,

INTRODUCTION

Liver performs central role in the transformation and metabolism of xenobiotic compounds, which in turn, results in various liver complications like ionic imbalance, formation of reactive metabolic species (RMS) causing oxidative stress, hindrance in signal transduction pathways, translational inhibition at multiple levels, Ca^{2+} shift and impairment of mitochondrial respiratory chain and β-oxidation. DIHT can lead to cholestasis, which in turn results in intrahepatic accumulation of toxic bile acids and excretion products, further promoting hepatic injury. Chronic hepatic diseases have emerged as major medical concern in recent days and hepatotoxicity due to drugs is among the major contributing factor in this regard [1]. In 2008, over 16,000 lives were lost in the UK due to liver diseases and 700 liver transplants are performed only in UK each year [2]. According to WHO report, 21,000 livers were transplanted in 2007 worldwide [3]. Therefore, safeguard of the hepatic system is of utmost importance from the physiological point of view.

Hepatotoxicity

In the context of DIHT, the words of Paracelsus, the father of toxicology that, "the dose makes the poison" seems to be most appropriate. There are more than 900 compounds marked as potent hepatotoxins [4]. Hepatotoxicity is one of the main reasons behind withdrawal of a drug from the market. 50% of all acute liver failures and 5% of all hospital admissions are associated with DIHT[4]. Liver transplantation is required and even death occurs as a results of idiosyncratic drug reactions in 75% of cases[5]. In the liver, bio-activation of these xenobiotics generates RMS, which reacts with cellular macromolecules leading to protein dysfunction, lipid peroxidation, DNA damage, and oxidative stress[6]. These RMS may further cause disruption of ionic gradients and intracellular Ca^{2+} storage resulting in mitochondrial dysfunction, which in turn releases harmful reactive oxygen species (ROS) causing tissue injury. Oxidative stress of hepatocytes may results in inflammation. ROS formed at the hepatocytes may stimulate activation of various immunoregulatory cells such as natural killer T (NKT) cells, Kupffer cells and natural killer (NK) cells. These cells further secret inflammatory cytokines such as tumour necrosis factor (TNF)-α, interferon (IFN)-γ, and interleukin (IL)-1β which promotes tissue damage[7]. On the other hand, study on the knockout of immunoregulators such as prostaglandins, IL-10 and IL-6 has shown easy susceptibility to hepatotoxicity. Therefore, it may be the delicate balance between the detoxification machinery and the immune regulators which determines an individual's susceptibility and adaptation to hepatic injury. A model of the various events which occur during DIHT is shown in the figure1

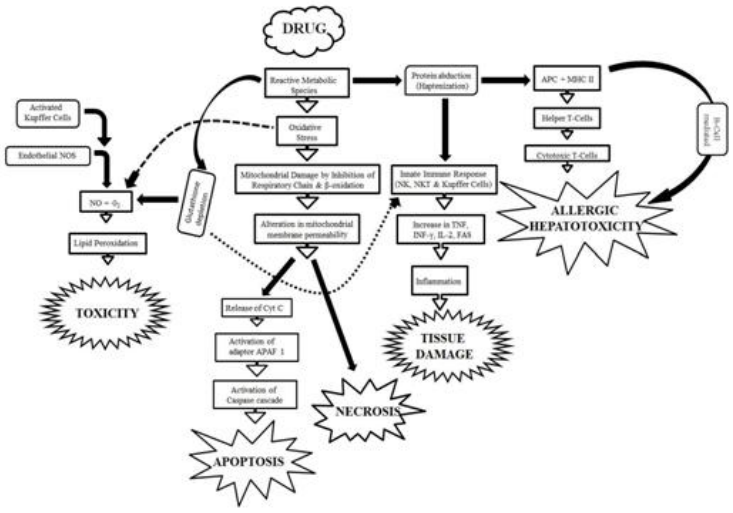

Figure 1: The figure displays the various events which occur during the DIHT. The reaction cascade starts with formation of reactive drug metabolic intermediate which can harm the hepatic system in various ways. By releasing the Cyt C, it may initiate the apoptotic pathway of it may induce hepatocellular necrosis by affecting the mitochondrial system. Activated Kupffer cells and endothelial nitric oxide synthase (NOS) may couple with the free oxygen radicals to subsequently form hepatic toxicity. Another arm of the downstream cascade leads to the activation of the immunoregulatory pathway, where it may cause direct inflammatory tissue damage by the innate immune response or it may results in T- cell mediated allergic hepatotoxicity.

Types of hepatotoxicity

Hepatotoxicity can be divided into three major categories and in general determined by three fold increases in alanine amino transferase (ALT) level i.e. glutamic oxaloacetic acid transaminase level, two fold increase in alkaline phosphatase (ALP) level and two fold increase in serum bilirubin (SBLN) level, if associated with increased ALT and ALP level[8]. Primarily elevation of ALT or ALP level is characterized as Hepatocellular injury; elevation of ALP and bilirubin level as Cholestatic and in mixed injury both ALT and ALP level increase[8]. **Table 1** show a list of various drugs associated with hepatotoxicity:

Table 1: Various drugs associated with various modes of hepatotoxicity

Hepatocellular Injury	Cholestatic Injury	Mixed Injury
Acetaminophen	Amoxicillin	Amitriptyline
Allopurinol	Anabolic steroids	Azathioprine
Amiodarone	Chlorpromazine	Captopril
Baclofen	Oral contraceptives	Clindamycin
Fluoxetine	Erythromycins	Cyproheptadine
Isoniazid	Estrogens	Enalapril
Ketoconazole	Mirtazapine	Nitrofurantoin
Lisinopril	Phenothiazines	Phenobarbital
Losartan	Terbinafine	Phenytoin
Methotrexate	Tricyclics	Sulfonamides
Omeprazole		Trazodone
Paroxetine		Verapamil
Pyrazinamide		
Rifampin		
Risperidone		
Tetracyclines		
Trovafloxacin		
Valproic acid		

Pathological Manifestations of DIHT

The mode of action of various drugs on the hepatic system is not the same. The following are the pathological manifestations of various hepatotoxic drugs on the liver[9]. Such as: Acute viral hepatitis (INH, halothane, diclofenac, troglitazone); Chronic hepatocellular injury (pemoline, methyldopa); Steatohepatitis (amiodarone, nifedipine, didanosine, synthetic estrogens); Massive necrosis (acetaminophen, halothane, diclofenac); Mononucleosis like condition (phenytoin, dapsone, sulphonamides); Seratosis (alcohol, methotrexate, TPN, nifedipine, corticosteroids, minocycline, tetracycline, valproic acid, piroxicam); Hepatocellular carcinoma (aflatoxin, arsenic, vinyl chloride, anabolic steroids); Cholestasis (amoxicillin-clavulanic acid, sulindac, erythromycin, tetracycline, chlorpromazine, sulfamethoxazole-trimethoprim, ibuprofen); Granulomatous hepatitis (tetracycline, chlorpromazine, sulfamethoxazole-trimethoprim, ibuprofen).

Acetaminophen and Hepatotoxicity

One of the highly studied cases of DIHT is of acetaminophen (also known as paracetamol), which accounts for worldwide highest number of drug-induced liver disease. Approximately 1000 cases of acute liver failure in United States are directly associated with DIHT, among which around 400 cases are due to acetaminophen toxicity and 130 cases due to idiosyncratic drug reactions[9]. Within the prescribed dose, though acetaminophen is well tolerated by the body, but overdose certainly results in acute liver damage. During the detoxification pathway, cytochrome P-450-2E1 reacts with acetaminophen and generates reactive metabolic intermediate N-acetyl-p-benzoquinone imine (NAPQI), which cause direct hepatotoxicity[10].

Standard hepatotoxic drugs and DIHT

Primarily due to hepatotoxicity, drugs such as nefazodone, trovafloxacin, troglitazone, ximelagatran, ebrotidine, pemoline were withdrawn from the market or given warnings [11]. DIHT has now emerged as the leading cause behind acute liver failure among the US patients. More than 10% of cases of acute liver failure are caused by idiosyncratic mediated hepatotoxicity[11].

Anti-tubercular drugs such as rifampicin, isoniazid and pyrazinamide are potentially harmful drugs causing hepatotoxicity and it has been estimated that anti-tuberculosis related hepatotoxicity is reported in 28% cases[12]. A vast array of non-steroidal anti-inflammatory drugs (NSAID) such as amphenac, benoxaprofen, bromofenac, cinchophen, fenclozic acid, fluproquazone, glafanine, isoxepac, pirprofenac, phenylbutazone, sudoxicam etc were withdrawn from the market as they caused hepatotoxicity[13] due to immunological idiosyncrasy[14]. Numerous aesthetic agents such as halothane, isoflurane, enflurane,

desflurane, chloroform, nitrous oxide have been found to cause direct hepatotoxicity (hepatocellular necrosis), immune mediated hypersensitivity, interference with bilirubin metabolism and cause cholestasis[15]. Anti-retroviral drugs (ARVD) very often elevate the liver transaminases level and are found to be associated with hepatotoxicity[16]. ARVD can be of several types depending on their mode of action[4]: nucleoside analogues reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, tenofovir), non-nucleoside analogues reverse transcriptase inhibitors (efavirenz, emtricitabine, nevirapine) and protease inhibitors (indinavir, nelfinavir, saquinavir). Anti-hyperlipidemic drugs such as atorvastatin, simvastatin, pravastatin, lovastatin, gemfibrozil also displays hepatotoxic behaviour and their mode of action includes oxidative stress, immune-mediated inflammation and tissue damage, impairment of mitochondrial P450 system and bile acid transport[4]. Carbamazepine, felbamate, valproic acid and phenytoin belong to a huge family anti-epileptic drugs which are transformed to some reactive metabolic intermediates resulting in direct hepatic toxicity[17]. Similar cases of DIHT can be found for many other class of drugs such as anti-psychotic drugs, anti-Hypertensive Drugs, acetylcholine esterase inhibitors, anti-depressants, antibiotics etc.

Case study

Troglitazone (rezulin) was commercialised as antidiabetic agent in 1997, but 90 reports of hepatotoxicity over a period of merely 3 years made FDA place a ban on the drug[18]. In the same year, a nonsteroidal anti-inflamatory drug bromfenac (duract) was introduces to the orthopaedic patients as short-term analgesic drug, overdose of which resulted in over 50 cases of severe hepatic injury and subsequently withdrawal of the drug in the next year. Another potent hepatotoxic drug pemoline (cylert) was approved by the FDA in 1975for narcolepsy and attention deflect disorders. Later it was withdrawn by all the manufacturing companies in 2005 after 21 confirmed cases of liver failure induced by pemoline. Ximelagatran (exanta) was initially tested as anticoagulant but alter on during the clinical trials it was detected that ximelagatran uptake elevates the liver enzymatic levels and cause hepatotoxicity. Thus, in 2004, FDA rejected all the applications for the commercialization of ximelagatran. Ticrynafen (tienilic acid) was approved by FAD in 1979 as anti- hypertension drug, but after several reports of liver failure and association of ticrynafen with hepatitis resulted in its withdrawal in 1982. An anxiolytic drug alpidem (ananxyl) was withdrawn in 1995 due to the same reason[20]. Other drugs that have limited usage due to similar hepatotoxic fingerprints are trovafloxacin (trovan), an antibiotic; tolcapone (tasmar), used to treat Parkinson disease; zileuton (zyflo), for asthma; felbamate (felbatol), used for partial seizures; isoniazid, an anti-tubercular drug; dantrium (dantrolene), used for malignant hyperthermia; normodyne (labetalol), used in high blood-pressure etc. Interferon β-1a (also known as rebif, avonex and cinnovex) is used in the treatment of multiple sclerosis and has been reported to cause severe liver injury, which even results in total liver failure[21]. The risk of hepatic injury multiplies several folds when interferon β-1a is administered in combination with alcoholic products. Thirty two cases of severe liver injury was reported in 2009 by FDA, all of which were propylthiouracil mediated. For safety precautions various pharmaceutical companies are now including warnings stating that certain drug might cause hepatotoxicity. Such as, the package insert of an anti-depressant drug duloxetine mentions that, "cymbalta (duloxetine) should not be administered to patients with substantial alcohol use or any hepatic insufficiency"[9].

Risk factors Associated With DIHT

Statistical analysis of the cases of DIHT patients show that there are several underlying risk factors associated, with whom toxic effects of various drugs can be correlated. Alcoholism cause depletion of glutathione and cirrhotic changes in the liver, which alters the drug metabolism pathway. Age of a person may also play a profound role in susceptibility to hepatotoxicity, like it has been observed that elderly persons are at increased risk of DIHT because of their age related reduced hepatic blood flow and hepatic volume, variation in drug binding and decrease in clearance mechanism. Genetic factors may also play profound role in the susceptibility to DIHT such as in the case of an antiarrhythmic drug debrisoquine, which gets poorly metabolised due to abnormal expression in cytochrome P-450-II-D6 gene. The following are some risk factors associated with DIHT[9]: male (Amoxicillin-clavulanic acid); female (Halothane, Nitrofurantoin, Sulindac); young age (salicylates, valproic acid); old age (halothane, acetaminophen, amoxicillin-clavulanic acid); obesity (halothane); renal failure (tetracycline, allopurinol); Diabetes mellitus (methotrexate, niacin); hepatitis C (Ibuprofen, flutamide, ritonavir); Malnutrition (acetaminophen); AIDS (dapsone, trimethoprim-sulfamethoxazole).

CONCLUSION

Drugs are for the treatment of diseases, but it's utility turns in vain if it shows toxic phenotype. There are several commercial drugs possessing hepatotoxic character. Therefore, the pharmaceutical companies now have turned their attention towards the herbal formulations for their therapeutic and hepatoprotective capacity. Plants such as turmeric[22] have shown potent hepatoprotective capacity against various hepatotoxic models. In most cases, the phytochemical content[23,24] of these plants play the major role in their hepatoprotective activity. Numerous plants have been screened for their possible hepatoprotective capacity[25]. Plants possessing potent antioxidant capacities such as *Nerium indicum*[26,27] have been tested for their hepatoprotective status as antioxidant capacity is a major determinant of hepatoprotective behaviour. With the ever increasing cases of DIHT, we can hope for better and reliable complementary and alternative medicines in the future.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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