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Chemicals/drugs-hepatotoxicants: An overview

Gurfateh Singh*, Deepika Bhatia and S. L. Harikumar

Department of Pharmacology, University School of Pharmaceutical Sciences, Rayat -Bahra University, Mohali, Punjab, India

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ABSTRACT

Hepatotoxicity is mainly caused by the inorganic compounds, organic agents and synthetic drugs. These inorganic compounds, organic agents and synthetic drugs which undergo metabolism in the liver and produces free radicals in the liver which causes liver damage. Drugs such as Statins, Methotrexate, Paracetamol, Alcohol etc are some common hepatotoxic agents. Approximately 75% of idiosyncratic drug reactions results in liver transplantation or death. These hepatotoxic drugs mainly increase the transaminase liver enzyme i.e. SGOT, SGPT and ALP level which is very much effective marker of liver disease. This review throws light on various drugs which induce hepatotoxicity with the overview of their common mechanism.

Keywords: Liver, Hepatotoxicity, Models.

INTRODUCTION

Liver Disease is a major cause of morbidity and mortality [1]. Liver injury is an extremely serious health problem in modern world. It is one of the largest organs in human body and the chief site for intense metabolism and excretion [2]. It is an injury to the liver that is associated with liver function caused by exposure to a drug or any other infectious agent. The liver plays a major role in clearing chemicals and is susceptible to the toxicity from these chemical agents. As per data survey more than 900 drugs, toxins, and herbs have been reported to cause hepatic cell injury. Approximately 75% of the idiosyncratic drug reactions result in liver transplantation or death. The chemicals that cause liver injury are called hepatotoxins. The occurrence of drug-induced hepatotoxicity is due to over consumption of alcohol, NSAIDS, anti-tubercular, anticancer and anticonvulsant drugs [3]. It has been noted as jaundice, cirrhosis, hepatitis, steatosis, fibrosis, liver cancer and ultimately leads to liver dysfunction [1]. Hepatotoxicity implies chemical driven liver damage. There are certain medicinal agents when taken in higher dose and sometime even in therapeutic range may damage the liver moreover some laboratories agents, laboratories chemicals, herbal remedies like CCL_4, Paracetamol, Ethanol, Lead, Arsenic, Ephedra, Microcystins, Aflatoxin can also induced hepatotoxicity [4,5]. It has been noted that hepatitis, hepatic necrosis and hepatic steatosis are main cause of hepatotoxicity [6]. Liver injury leads to disturbance in transport function of hepatocytes resulting in leakage of plasma membrane which results in increased the level of SGOT, SGPT and bilirubin enzyme clinically and pre-clinically [7,8] due to up regulation of TNF-α, interleukin-1, interleukin-10 [9], TGF- beta-1 [10], collagen and kuffer cell. Moreover the opening of MPTP (membrane permeability transition pore) [11] and DNA damage has been noted in the experimental hepatotoxicity. The level of oxidative stress also increased in the experimental hepatotoxicity. These above programs lead to necrosis of liver cell. There are various experimental models are employed to induced hepatotoxicity in order to identify the noble pharmacological approaches for hepatotoxicity. The present review focused on various chemicals induced experimental hepatotoxicity.

CHEMICALS-DRUGS FOR MODEL OF HEPATOTOXICITY

Carbon tetrachloride induced hepatotoxicity

Liver injury due to carbon tetrachloride in rats was first reported in 1936 and has been widely used by many investigators. Carbon tetrachloride (CCL_4) is metabolized and activated by cytochrome $(CYP)_2E_1$, CYP_2B_1 or CYP_2B_2, and possibly CYP_3A, in endoplasmic reticulum and mitochondria with the formation of CCl_3O-, a reactive oxidative free radical [12]. At the molecular level CCl_4 activates tumor necrosis factor (TNF) alpha, nitric oxide (NO), Caspases-2 and transforming growth factors (TGF)-alpha and –beta shown the destruction of hepatic cells processes that appear to direct the cell primarily toward destruction or fibrosis. TNF alpha leads to apoptosis, whereas the TGFs appear to direct toward fibrosis [13]. Recent studies shown that the Dose of CCl_4 (2 ml/kg, *s.c.*) at every 72 h for 10 days and single dose of CCl_4 (2.3ml/kg *i.p)* produced hepatotoxicity [14]. The acute toxicity observed at the dose administration on 7th day of experiment cause centrilobular necrosis and fatty changes has been observed. The development of necrosis is associated with leakage of hepatic enzymes into serum [15]. The administration of CCL_4 at the dose of 3gm/kg via intra gastric tube for three week produced necrosis [16].

Thioacetamide induced hepatotoxicity

Thioacetamide (TAA) is an organo sulphate compound white crystalline solid in colour which is soluble in water. After the administration of drug it is selective hepatotoxins with in a short period of time. TAA induced acute and chronic liver injury due to its effects on protein synthesis, RNA, DNA and Gamma-glutamyl transpeptidase activity [17]. TAA undergoes two-step bio activation to sulfine, and after then to sulfene, a reactive metabolite. Sulfine is responsible for the enlargement of nucleoli, increase in nuclear volume and intracellular concentration of Ca^{++} that will lead to cell damage [18]. At the same time Sulfene is responsible for the release of nitric oxide synthase and NF-kappa B directing to centrilobular necrosis, protein denaturation and lipid peroxidation [19]. TAA affects the movement of RNA to cytoplasm from nucleus which may cause injury to the cell membrane. TAA metabolite (perhaps s-oxide) is responsible for hepatic injury. TTA decreases the number of viable hepatocytes as well as rate of oxygen consumption. It also decreases the volume of bile and its content i.e. bile salts, cholic acid and deoxycholic acid. As per latest study the administration of TAA at the dose of 200mg/kg *i.p*. twice a week for 8 weeks produced cerebral necrosis [20,21].

Galactosamine induced hepatotoxicity

Galactosamine is a well establish hepatoxicant. It produces diffuse type of liver injury and stimulating viral hepatitis. It presumably disrupts the synthesis of essential uridylate nucleotides resulting in organelle injury and ultimately cell death. Depletion of those nucleotides would impede the normal synthesis of RNA and consequently would produce depletion in protein synthesis [22]. This mechanism of toxicity brings about an increase in cell membrane permeability leading to enzyme leakage and eventually cell death. The cholestasis caused by galactosamine may be from its damaging effects on bile ducts or ductules or canalicular membrane of hepatocytes. It has been observed that galactosamine reduces the number of viable hepatocytes as well as rate of oxygen consumption. It has been observed that single dose of D-glactosamine 800 mg/kg *i.p* administration on 21 days of experiment and dose of D-glactosamine 500 mg/kg *i.p* three times weekly over a period of one to three month induced hepatotoxicity. [23]

Alcohol induced hepatotoxicity

Liver is among the organs most susceptible to the toxic effects of alcohol. Alcohol consumption is known to cause fatty infiltration, hepatitis and cirrhosis. Fat infiltration is a reversible phenomenon that occurs when alcohol replaces fatty acids in the mitochondria. Hepatitis and cirrhosis may occur because of enhanced lipid per oxidative reaction during the microsomal metabolism of alcohol. The effects of ethanol can enhance generation of oxy free radicals during its oxidation in liver. This result in elevated levels of glutamyl transpeptidase, a membrane bound enzyme in serum. The decreased activity of antioxidant enzymes superoxide dismutase, glutathione peroxidase are speculated to be due to the damaging effects of free radicals produced following ethanol exposure or alternatively could be due to a direct effect of acetaldehyde, formed by oxidation of ethanol [24]. It is observed that ethanol: 3g/kg body weight or 30% v/v *p.o.* for 20 days induced hepatotoxicity. The initial dose of ethanol was 6g/kg/day (solution maximally containing 56% alcohol) and the dose was progressively increased during week 1 to a maintenance dose of 8g/kg/day that was continued for 5 more weeks induced hepatotoxicity [25, 26].

Paracetamol induced hepatotoxicity

Paracetamol (PCM) is a widely used anti-pyretic and analgesic, produces acute liver damage if overdoses or some time therapeutic dose is consumed. Paracetamol overdose can cause severe hepatotoxicity and even liver failure in

experimental animals and humans. One consequence of this is an inhibition of mitochondrial respiration, ATP depletion and mitochondrial oxidant stress. In the presence of sufficient vitamin E reactive oxygen formation does not induce severe lipid peroxidation but the superoxide reacts with nitric oxide to form peroxynitrite, a powerful oxidant and nitrating agent. Peroxynitrite can modify cellular macromolecules and may aggravate mitochondrial dysfunction and ATP reduction leading to cellular oncotic necrosis in hepatocytes and sinusoidal endothelial cells [11]. Thus, we hypothesize that reactive metabolite formation and protein binding initiate the injury process, which may be then propagated and amplified by mitochondrial dysfunction and peroxynitrite formation. It has been observed that the 3g/kg, *p.o*. dose of PCM given on 3rd and 5th day of 7th day experiment induced hepatotoxicity [27]. Moreover single dose of PCM (3gm/kg.*p.o.)* administered on 3rdday of experiment [28] or single dose of PCM (2gm/kg *p.o.)* on 5th day of experiment induced hepatotoxicity [29].

Methotrexate induced hepatotoxicity

Methotrexate (MTX) is a first-line drug used in the management of early and established arthritis. MTX can induce a variety of histologic changes including steatosis, stellate cell hypertrophy and hepatic fibrosis [30]. MTX is a folate analog that enters the cell bound to folate trasporter 1 and is pumped out by the ATP-binding cassette (ABC) family of transporters. Methotrexate is retained with in the cell as a polyglutamate that inhibits dihydrofolate reductase, thymidylate synthase and AICAR (5-aminoimidazole-4-carboxamide ribonucleotide) transformylase, leading to impaired pyrimidine and purine synthesis. In addition, methotrexate indirectly affects MTHFR (methylene-tetrahydro folate reductase) and hence the generation of methionine from homocysteine. Methotrexate therapy in patients with rheumatoid arthritis has been shown to raise plasma homocysteine levels, although this effect varies depending on concurrent administration of folate. Excess homocysteine can generate oxidative stress or sensitize the cell to its cytotoxic effects. Homocysteine has been shown to induce endoplasmic reticulum (ER) stress, which, when unresolved, leads to fatty infiltration of the liver. Homocysteine, in addition, can also activate pro inflammatory cytokines results in activation of hepatic stellate cells, which leads to liver fibrosis [31]. Use of MTX for neoplastic diseases has been associated with abnormalities of liver biochemical tests. It is noted that dose of MTX 0.250 mg/kg body weight *i.p. g*iven for 4 weeks to animal responsible to induced necrosis in liver cell [32].

Azathioprine induced hepatotoxicity

Azathioprine (AZA) is an important drug used in the therapy of autoimmune disorders and in preventing draft rejection Azathioprine can also cause an acute, clinically apparent liver injury that is typically cholestatic. The mechanism of AZA toxicity to mitochondrial injury found depletion of ATP and cell death by necrosis. Lipid peroxidation as well as altered level of some endogeneous scavenger is taken as indirect in vivo reliable indices for the contribution of free radical generation and in turn oxidative stress [33] Elevated thiopurine methyltransferase activity leading to hyper-methylation has been considered a potential mechanism of hepatotoxicity. Alternatively, oxidation of azathioprine or 6-mercaptopurine by xanthine oxidase might be associated with the generation of reactive oxygen species, thus contributing to liver injury [34]. The recent data told that after 48 h of treatment with azathioprine at the high concentration of 50 micron causes GSH depletion [35].

Rifampicin induced hepatotoxicity

Rifampicin is a macro cyclic antibiotic. Patients on concurrent Rifampicin therapy have an increased incidence of hepatitis. This has been postulated due to Rifampicin-induced cytochrome P450 enzyme-induction, causing an increased production of the toxic metabolites from acetyl hydrazine (AcHz). The mechanism of rifampin hepatotoxicity is not well known but it is extensively metabolized by the liver and induces multiple hepatic enzymes including CYP 3A4 and ABC C2 (MRP2). Thus, the Rifampicin also increases the metabolism of INH to be nicotinic acid and hydrazine, both of which are hepatotoxic. Rifampicin also interacts with antiretroviral drugs and affects the plasma levels of these drugs as well as risk of hepatotoxicity [36]. However isoniazid (INH, 50 mg/kg, po) and rifampicin (RMP, 100 mg/kg, *p.o.*) combination is also induced hepatotoxicity [37].

Isoniazid induced hepatotoxicity

Isoniazid (INH) is a potent anti-mycobacterial agent which is thought to act by inhibition of lipid and DNA synthesis of mycobacterium tuberculosis, thus inhibiting its cell wall synthesis. Hepatotoxicity is a common complication of antimicrobial and anti-tuberculosis therapy that ranges in severity from asymptomatic elevation of serum transaminases to hepatic failure requiring liver transplantation. This is not caused by high plasma Isoniazid levels but appears to represent an idiosyncratic response. INH is metabolized to mono acetyl hydrazine, which is further metabolized to a toxic product by cytochrome P450 leading to hepatotoxicity. Human genetic studies have shown that cytochrome P4502E1 (CYP2E1) is involved in antitubercular drug hepatotoxicity [38]. The CYP2E1

c1/c1 genotype is associated with a higher CYP2E1 activity and may lead to a higher production of hepatotoxins. INH has an inhibiting effect on CYP1A2, 2A6, 2C19 and 3A4 activity. Isoniazid can induce its own toxicity, possibly by the induction or inhibition of these enzymes [39, 40]. The dose of INH i.e. 27mg/kg, *p.o.* for 30 days [41] and 50 mg/kg *p.o* for 7 days produced hepatotoxicity [42].

Mercuric chloride induced hepatoxicity

Our human activities play a major role in polluting the environment by toxic and carcigenic metal compound. These metals are accumulated in the water and food. Mercury is widely used in the industries and also hazard to animals has been reported. It is a transition metal and it promotes ROS generation such as hydrogen peroxide. The ROS increase the generation of hydrogen and peroxide radicals. Mercury as inhibits the enzymes such as superoxide dismutase and glutathione peroxidase. It causes cell membrane damage and ROS generation cause alteration in mitochondria by alter mitochondrial permeability transition pore [43]. The dose of mercuric chloride 5mg/kg *i.p.* for twenty days induced necrosis and 2mg/kg orally for thirty days produced hepatotoxicity [44].

Bromobenzene induced hepatotoxicity

Bromobenzene (BB) is a solvent used in industries cause necrosis of liver. It is a subject to biotransformation in liver and metabolism of BB is highly toxic. BB is hydrolyzing by cytochrome p450 mono-oxygenase and inhibitor of cytochrome p450 monooxygenase was found to induce hepatotoxicity. This leads to a number of secondary events that damage the cell, like lipid peroxidation, ATP depletion, mitochondrial dysfunction, energy imbalance and alteration in intracellular calcium level result liver damage [45]. It has been observed that the administration of BB (0.5, 2.0 and 5.0 mmole/kg, *p.o*) for 10-12 weeks induced hepatotoxicity [46].

CONCLUSION

Hepatotoxicity implies chemical drive liver damage. The list of hepatotoxic drugs and chemicals are huge and a complete coverage of all these drugs/chemicals is difficult. Some drugs/chemicals are sum up in the above review article with their common overview regarding theirs pathological factors responsible for hepatotoxicity in preclinical and clinical scenario. These agents/chemicals produced hepatotoxicity when they are given at higher dose and even at therapeutic dose induced hepatotoxicity due to the generation of free radical, oxidative stress and alter the Mitochondria permeability transition pore. Hence, it can be concluded that the better understanding of the chemicals/drugs involved in experimental hepatotoxicity would help to define new therapeutic strategies to elucidate newer hepatoprotective drugs.

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