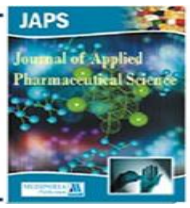
Journal of Applied Pharmaceutical Science 02 (05); 2012: 233-243

Journal of Applied Pharmaceutical Science

Available online at www.japsonline.com



ISSN: 2231-3354
Received on: 23-11-2011
Revised on: 09:12:2011
Accepted on: 13-12-2011
DOI: 10.7324/JAPS.2012.2541

Drug-Induced Hepatotoxicity: A Review

Aashish Pandit, Tarun Sachdeva and Pallavi Bafna

Aashish Pandit, Tarun Sachdeva and Pallavi Bafna
Rayat Institute of Pharmacy, Railmajra, Distt. S.B.S. Nagar, Punjab, Pin: 144533, India.

For Correspondence
Dr. Pallavi Bafna
Professor of Pharmacology, Rayat Institute of Pharmacy, Railmajra, Dist. Nawanshahar, Punjab -144533 (INDIA). Tel: +91-8146446996

ABSTRACT

Liver is the principle organ for maintaining the body's internal environment. There is currently no way to reimburse for the absence of liver function. Its major influence is on the flow of nutrients and controls the metabolism of carbohydrate, protein and fats. Drugs are an important cause of liver injury. More than 900 drugs, toxins, and herbs have been reported to cause liver injury. Approximately 75% of the idiosyncratic drug reactions result in liver transplantation or death. Various types of drug induced liver diseases are acute-dose dependent liver damage, acute fatty infiltration, cholestatic jaundice, liver granulomas, active chronic hepatitis, liver cirrhosis, liver tumors etc. In the United States, approximately 2000 cases of acute liver failure occur annually and drugs account for over 50% of them (37% are due to acetaminophen, 13% are idiosyncratic reactions due to other medications). Drugs account for 2-5% of cases of patients hospitalized with jaundice and approximately 10% of all cases of acute hepatitis. Chronic liver disease and cirrhosis account for some 2% of mean in 17 countries with nearly 40,000 deaths per year. Considering the importance of drug-induced hepatotoxicity as a major cause of liver damage, this review throws light on various drugs which induce hepatotoxicity, with their mechanism of liver damage and clinical scenario.

Keywords: Liver, hepatotoxicity, drug, mechanism.

INTRODUCTION

The liver plays an astonishing array of vital functions in the maintenance, performance and regulating homeostasis of the body. It is involved with almost all the biochemical pathways to growth, fight against disease, nutrient supply, energy provision and reproduction (Sharma *et al.*, 1991). The major functions of the liver are carbohydrate, protein and fat metabolism, detoxification, secretion of bile and storage of vitamin. Thus, to maintain a healthy liver is a crucial factor for the overall health and well being (Subramaniam and Pushpangadan, 1999).

Hepatotoxicity implies chemical-driven liver damage. Certain medicinal agents, when taken in overdoses and sometimes even when introduced within therapeutic ranges, may injure the organ. Other chemical agents, such as those used in laboratories and industries, natural chemicals (e.g., microcystins) and herbal remedies can also induce hepatotoxicity. Chemicals that cause liver injury are called hepatotoxins. More than 900 drugs have been implicated in causing liver injury and it is the most common reason for a drug to be withdrawn from the market. Chemicals often cause subclinical injury to liver which manifests only as abnormal liver enzyme tests. Drug-induced liver injury is responsible for 5% of all hospital admissions and 50% of all acute liver failures. More than 75 percent of cases of idiosyncratic drug reactions result in liver transplantation or death (Ostapowicz *et al.*, 2002).

HEPATOTOXIC DRUGS

Anti-Tubercular Drugs

The first line anti-tubercular drugs namely, Rifampicin, Isoniazid and Pyrazinamide are potentially hepatotoxic drugs. These drugs are metabolized by the liver. No hepatotoxicity has been described for Ethambutol or Streptomycin. Adverse effects of antitubercular therapy are sometimes potentiated by multiple drug regimens. Thus, though INH, Rifampicin and Pyrazinamide each in itself are potentially hepatotoxic, when given in combination, their toxic effect is enhanced. Based on hepatotoxicity diagnosis criteria and population under study, incidence of anti-TB related hepatotoxicity is reported from 2% to 28% (Girling, 1978).

Rifampicin

Patients on concurrent Rifampicin therapy have an increased incidence of hepatitis. This has been postulated due to Rifampicin-induced cytochrome P_{450} enzyme-induction, causing an increased production of the toxic metabolites from acetyl hydrazine (AcHz). Rifampicin also increases the metabolism of INH to isonicotinic acid and hydrazine, both of which are hepatotoxic. The plasma half life of AcHz (metabolite of INH) is shortened by Rifampicin and AcHz is quickly converted to its active metabolites by increasing the oxidative elimination rate of AcHz, which is related to the higher incidence of liver necrosis caused by INH and Rifampicin in combination. Rifampicin also interacts with antiretroviral drugs and affects the plasma levels of these drugs as well as risk of hepatotoxicity (Padma *et al*., 1998; Tostmann *et al*., 2008).

Isoniazid

Isoniazid hepatotoxicity is a common complication of antituberculosis 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 monoacetyl hydrazine, which is further metabolized to a toxic product by cytochrome P_{450} leading to hepatotoxicity. Human genetic studies have shown that cytochrome P4502E1 (CYP2E1) is involved in anti tubercular drug hepatotoxicity (Huang *et al.*, 2003). The CYP2E1 c1/c1 genotype is associated with a higher CYP2E1 activity and may lead to a higher production of hepatotoxins. Rat studies showed that Isoniazid and Hydrazine induce CYP2E1 activity (Jenner and Timbrell, 1994; Jenner and Timbrell, 1995). Isoniazid has an inhibiting effect on CYP1A2, 2A6, 2C19 and 3A4 activity. CYP1A2 is suggested to be involved in hydrazine detoxification. Isoniazid can induce its own toxicity, possibly by the induction or inhibition of these enzymes (Wen *et al*., 2002; Desta *et al*., 2001).

Pyrazinamide

Pyrazinamide (PZA; pyrazoic acid amide) is converted to pyrazinoic acid and further oxidized to 5-hydroxypyrazinoic acid by xanthine oxidase. The serum half-life of pyrazinamide is not related to the length of treatment, indicating that pyrazinamide does not induce the enzymes responsible for its metabolism. The mechanism of pyrazinamide-induced toxicity is unknown; it is unknown what enzymes are involved in pyrazinamide-toxicity and whether toxicity is caused by pyrazinamide or its metabolites. In a rat study, pyrazinamide inhibited the activity of several CYP450 isoenzymes (2B, 2C, 2E1, 3A), but a study in human liver microsomes showed that pyrazinamide has no inhibitory effect on the CYP450 isoenzymes (Maffei and Carini, 1980; Nishimura *et al.*, 2004).

Non Steroidal Anti-Inflammatory Drugs

Acetaminophen, Nimesulide, Diclofenac, Ibuprofen are Non-steroidal anti-inflammatory drugs (NSAIDs) which are the centerpiece of pharmacotherapy for most rheumatological disorders, and are used in large numbers as analgesics and antipyretics, both as prescription drugs and over the counter purchases. It is the most important cause of the drug induced toxic injury to several organ systems, including well known injury to gastrointestinal tract and kidneys. In overdose, the analgesic/antipyretic acetaminophen produces centrilobular hepatic necrosis (Walker, 1997). The epidemiological risk of clinically apparent liver injury is low (1–8 cases per 100 000 patient years of NSAID use), but when it occurs, it can be serious and can cause diagnostic confusion (Sgro *et al.*, 2002). However, use of ibuprofen rose rapidly between 1998 and 2000. Nearly all of the NSAIDs have been implicated in causing liver injury, and tend to be hepatocellular in nature: the mechanism is thought to be immunological idiosyncrasy (Zimmerman, 1990). Several NSAIDs have been withdrawn from clinical use because of associated hepatotoxicity (Connor *et al.*, 2003). The new more selective COX-2 inhibitors (e.g. celecoxib, rofecoxib, nimesulide) are also associated with hepatotoxicity (Benichou, 1990), although celecoxib is said to have less potential for hepatotoxicity.

Examples of NSAID's of various classes withdrawn or abandoned due to hepatotoxicity (Lewis, 2003):

Anthranilic acid derivatives: Cinchophen and Glafanine.

Acetic acid derivatives: Amphenac, Fenclozic acid, Isoxepac and Bromofenac.

Propionic acid derivatives: Benoxaprofen, Ibufenac, Pirprofenac, Suprofenac and Fenbufen.

Pyrazolone derivatives: Phenylbutazone, Oxyphenbutazone

Oxicams: Isoxicam, Sudoxicam.

Quinazonlone derivatives: Fluproquazone.

Mechanism of toxicity of NSAID's

Recently, a number of *in vitro* animal models have been used to investigate the possible mechanisms of NSAID's-related hepatotoxicity. Studies using rat liver mitochondria and freshly isolated rat hepatocytes showed that diphenylamine, which is common in the structure of NSAID's, uncouples oxidative phosphorylation, decreases hepatic ATP content and induces hepatocyte injury. Incubation of mitochondria with diphenylamine, mefenamic acid or diclofenac caused mitochondrial swelling. In addition, a spectral shift of the safranine-binding spectra to

mitochondria occurred, indicating the loss of mitochondrial membrane potentials (one of the characteristics of uncoupling of oxidative phosphorylation). Addition of oligomycin, which blocks ATPase, protected against cell injury. In diclofenac-induced toxicity in hepatocytes, no significant oxidative stress (decrease in glutathione and lipid peroxidation) or increase in intracellular calcium concentration was seen. Paracetamol administration causes necrosis of the centrilobular hepatocytes characterized by nuclear pyknosis and eosinophilic cytoplasm followed by large excessive hepatic lesion. The covalent binding of N-acetyl-P-benzoquinoneimine, an oxidative product of paracetamol to sulphydryl groups of protein, result in lipid peroxidative degradation of glutathione level and thereby, produces cell necrosis in the liver (*Masubuchi et al., 2000; Bort et al., 1999*).

Diclofenac Voltaren

Diclofenac hepatotoxicity is an archetype of idiosyncratic DILI (Drug induced liver injury) (Mitchell *et al.,* 1973). About 15% of those patients regularly taking diclofenac develop elevated levels of liver enzymes, and a threefold rise in transaminase levels has been reported in 5%. Diclofenac is associated with a predominantly hepatocellular pattern of liver injury, but a cholestatic pattern of liver injury and cases resembling autoimmune hepatitis have also been described (Aithal, 2004). In addition to 4′-hydroxylation by cytochrome P450 2C9, diclofenac undergoes glucuronidation by UDP-glucuronosyltransferase-2B7 to form an unstable acyl glucuronide. The latter undergoes further oxidation by CYP2C8. In addition, CYP2C8 catalyzes the formation of 5-hydroxydiclofenac. Both diclofenac acyl glucuronide and benzoquinone imines derived from 5-hydroxydiclofenac modify proteins covalently; hence, decreased as well as increased activity of CYP2C8 potentially increase the risk of hepatotoxicity. MRP2 is involved in the transport of diclofenac acyl glucuronide to biliary canaliculi and the metabolite accumulates with decreased expression of MRP2. Accumulation of reactive metabolites generates oxidative stress and mitochondrial permeability transition, leading to cellular injury. In addition, covalent binding of reactive metabolites to 'self' proteins results in the formation of neoantigens. Mild liver injury in a susceptible individual and in a proinflammatory cellular environment could progress to serious DILI, or diclofenac adducts released from dying hepatocytes might be phagocytosed by APCs and presented with MHC II molecules. Recognition of neoantigens by helper T cells leads to their activation and an effector-cell response. Hepatocytes express MHC I molecules on their surface (which is further increased with inflammation) and may present diclofenac adducts, leading to cytotoxic T-cell mediated liver injury. Alternatively, B cells may recognize diclofenac adducts on the plasma membrane of hepatocytes, leading to their maturation into plasmacytes, the secretion of antibodies and immunological destruction of hepatocytes. Abbreviations: APC, antigen presenting cell; DILI, drug-induced liver injury; IL, interleukin; MRP2, multidrug resistance protein 2; TCR, T-cell receptor (Aithal, 2011).

Sulindac

Sulindac has been the drug most consistently associated with hepatotoxicity. Published reports consist of 91 cases of liver injury, with 43% showing a cholestatic pattern (Liver injury leads to impairment of bile flow and cases are predominated by itching and jaundice), 25% a hepatocellular pattern and the rest a mixed pattern of injury (Tarazi *et al.,* 1993).The majority of the patients (67%) were jaundiced and four patients died. Sulindac competitively inhibits canalicular bile salt transport, and such inhibition may contribute to cholestatic liver injury (*Bolder et al., 1999).*

Anti-Retroviral Drugs

Several anti-retrovirals have been reported to cause fatal acute hepatitis; they most often cause asymptomatic elevations of transaminases. Liver toxicity is more frequent among subjects with chronic hepatitis C and/or B. The incidence of drug induced liver toxicity is not well known for most anti retrovirals (Nunez, 1999). Liver toxicity, especially severe toxicity, is clearly more frequent in HCV (Hepatitis C) and/or HBV (Hepatitis B) co-infected individuals treated with HAART (Highly active antiretroviral therapy usually combination of two or three drugs) (Sulkowski *et al.,* 2000; Wit *et al.,* 2002).

Protease inhibitors

Examples: Ritonavir, Indinavir, Saquinavir, Nelfinavir Hepatotoxicity became more evident after the introduction of ART (Anti-retrovirals) of high activity, which initially included invariably a protease inhibitor (PI). However; none of the studies has been able to prove the higher potential for liver toxicity of this particular family of drugs. Among the PI, in some studies full-dose ritonavir (RTV) has been found to be more hepatotoxicity (Bonfanti *et al.,* 2001), although these results have not been confirmed by others (Cooper, 2002; Aceti, 2002). In certain cases, RTV has caused fatal acute hepatitis (Pai *et al.,* 2000). Several cases of liver toxicity associated with the use of indinavir (IDV) and saquinavir (SQV) have also been reported (Sulkowski, 2003). Nelfinavir was found to be less hepatotoxic than the other PI anlyzed (RTV, IDV, SQV amprenavir (APV) in study evaluating 1052 patients (Sulkowski, 2003; Kontorinis, 2003).

Nucleoside analogues reverse transcriptase inhibitors (NRTI)

Examples: Lamivudine (3TC), Tenofovir, Zidovudine, Didanosine, Stavudine, Abacavir (ABC) and Tenofovir (TDF). Some studies have found a lower incidence of hepatotoxicity with lamivudine (3TC) and tenofovir (Nunez *et al.,* 2001). However, the majority of the NRTI can induce mitochondrial damage, and, therefore, have a potential for the development of liver injury. Cases of hepatic failure have been reported in patients taking zidovudine, but didanosine and stavudine have been most often involved in severe hepatotoxicity. Abacavir (ABC) and tenofovir (TDF), with low potential for mitochondrial damage, seem to have a safer profile regarding the liver. In patients with chronic

hepatitis B, the removal of 3TC may be accompanied by a flare of HBV replication, translated into an increase in transaminases (Brinkman *et al.*, 1998).

Non-nucleoside analogues reverse transcriptase inhibitors

Examples: Nevirapine, Emtricitabine, Efavirenz. The risk of liver toxicity associated with the non nucleoside analogues reverse transcriptase inhibitors (NNRTI) is variable and involves several aspects and mechanisms. Several cases of severe liver toxicity, some of which were fatal in subjects receiving NVP (Nevirapine) as part of a post-exposure prophylaxis regimen (Bissuel *et al.*, 1994; Gisolf *et al.*, 2000) were reported. While some authors have found a higher risk of liver toxicity for NVP compared to efavirenz (EFZ), others have failed to do so. It is interesting that one of the studies did not find cross hepatotoxicity between NVP and EFZ (Sulkowski, 2002; Palmon, 2002). In the same study, the morbidity and mortality derived from liver toxicity among patients taking NVP or EFZ was similar. Moreover, in a study assessing NVP hepatotoxicity, transaminases decreased in many of the patients who continued taking the same treatment (Carbonero *et al.*, 2002; Martinez *et al.*, 2001).

Mechanism of toxicity of Antiretrovirals

The possible mechanisms involved in the development of hepatotoxicity associated with the use of antiretrovirals are summarized below. It is probable that multiple pathogenic pathways simultaneously concur in some patients, being difficult to identify the exact mechanisms involved in the development of hepatotoxicity.

Direct toxicity

Anti-retrovirals, as any other drug, can induce direct toxicity in the liver. Drugs metabolized in the liver through the cytochrome pathways may cause liver toxicity when there are polymorphisms in the enzymes (Bissell *et al.*, 2001). Since many of the anti-retrovirals are metabolized in the liver through the cytocrome pathways, idiosyncratic polymorphisms of the enzymatic complexes might lead to significant heterogeneity in drug metabolism, predisposing to the development of hepatotoxicity in certain individuals. Some drugs may potentiate the activation of death receptors and/or intracellular stress pathways (Leist *et al.*, 1998).

Hypersensitivity reactions

Hypersensitivity reactions are idiosyncratic reactions of the host, not related to the dose of the drug. Immune mediated drug reactions seem to involve the generation of neoantigens formed by the reaction of liver proteins with reactive drug metabolites. Hypersensitivity reactions have been reported relatively often with NVP and abacavir (ABC), both in HIV-infected patients and in subjects receiving prophylaxis after HIV exposure (Johnson, 2002; Walker, 2002), but also with other antiretrovirals such as zalcitabine (ddC).

Mitochondrial toxicity

It is infrequent but a distinctive type of hepatotoxicity that may evolve to acute liver failure. The main feature of the hepatic lesion is the accumulation of micro vesicular steatosis in liver cells and mitochondrial depletion. This early lesion may evolve to macro vesicular steatosis with focal necrosis, fibrosis, cholestasis, proliferation of biliary ducts, and Mallory bodies, a clinical picture resembling alcohol induced liver toxicity, pregnancy steatosis or Reye's syndrome. Of interest, the underlying liver disease does not predispose to this type of lesion (Bissell *et al.*, 2001). It is believed that the cumulative exposure to NRTI is an important factor for the development of lactic acidosis, since it usually appears after prolonged treatment, usually years, and correlates with the number of concomitant NRTI. In vitro data support an additive or synergistic long-term mitochondrial toxicity with some NRTI combinations (Chitturi and George, 2002).

Anti-Hyperlipidemic Drugs

The pattern of liver injury from anti-hyperlipidemics is typically hepatocellular or mixed in nature with rare instances of pure cholestatic picture (Bertolami, 2007). The proposed mechanisms of hepatotoxicity are varied depending on the drug or drug class, and include effects on the cytochrome P450 system, impairment of bile acid transport proteins, immune-mediated inflammatory response to the medication or its metabolites, immune-mediated apoptosis by tumor necrosis factor, and oxidative stress due to intracellular damage. The anti-hyperlipidemic drug with the highest potential for hepatic injury is the sustained-release formulation of niacin. HMG CoA reductase inhibitors, otherwise known as statins, very rarely cause clinically significant liver injury, although asymptomatic elevation in amino transferases is common (Cohen *et al.*, 2006).

Statins

Statins competitively inhibit 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase, an enzyme necessary for cholesterol biosynthesis; they also act in several ways to decrease the level of low density lipoprotein (LDL) and increase the stability of atherosclerotic plaques (Jacobson, 2006). Initial studies of statins performed on animals revealed that very high doses of statins may cause hepatotoxicity, but typical therapeutic doses of the drug were not associated with significant liver injury (Horsmans *et al.*, 1990). High doses of lovastatin caused significant hepatocellular necrosis in rabbits. This pattern of injury was also seen in a guinea pig model exposed to high doses of simvastatin. However, hepatocellular necrosis from statins is exceptionally rare in humans (Alonso *et al.*, 1999).

Atorvastatin

Atorvastatin-related hepatotoxicity has been associated with a mixed pattern of liver injury typically occurring several months after the initiation of the medication (Nakad *et al.*, 1999;

Pelli *et al.*, 2003). There has also been a recent case report of underlying autoimmune hepatitis apparently revealed by atorvastatin. After broad experience with this medication (hundreds of thousands of treated patients), significantly increased transaminases levels greater than 3 times the upper limit of normal were only seen in 0.7% of cases (Grimbert *et al.*, 2006).

Lovastatin

Mixed hepatic injury in hepatocellular and cholestatic patterns has also been noted with the use of Lovastatin. This type of liver injury covers damage with varying proportions of cytotoxic and cholestatic involvement. Direct effect or productions by enzyme–drug adduct leads to cell dysfunction, membrane dysfunction cytotoxic T-cell response. One reported case in which a liver biopsy was done revealed histologic findings of centrilobular necrosis and cholestasis with a mixed inflammatory infiltrate (Ricaurte *et al*., 2006).

Simvastatin

Simvastatin hepatotoxicity is hypothesized to occur due to drug-drug interactions 1) There have been case reports describing hepatotoxicity when simvastatin is used in conjunction with flutamide, troglitazone, and diltiazem (Kanathur, 2001; Caldwell, 2001).

Pravastatin

Pravastatin has been reported to cause acute intrahepatic cholestasis. In this case, liver toxicity occurred within 2 months after initiating the drug and it resolved within 2 months after its discontinuation (Dalton and Berry, 1992).

Niacin

Unsupervised use of the sustained-release formulation of niacin often leads to its dose-related toxicity and should be discouraged (Etchason *et al.*, 1991). The onset of hepatotoxicity generally appears anywhere from 1 week to 48 months after the initiation of the drug and usually subsides with discontinuation. The typical pattern of injury involves an elevation in amino transferase levels although a mixed pattern of hepatocellular and cholestatic injury can be seen (Hodis, 1990; Chen, 1994)

Fibrates

Several studies have linked clofibrate and gemfibrozil to hepatomegaly, hepatocyte apoptosis, and hepatocarcinogenesis in rodent models (Dix *et al.*, 1999; Reimund and Ramos, 1994).

Ezetimibe

Recent studies have noted that ezetimibe may rarely cause hepatotoxicity in the form of severe cholestatic hepatitis and acute autoimmune hepatitis. The mechanism of toxicity may be related to the metabolism of the drug; it is rapidly absorbed and glucuronidated, yielding an active metabolite and there is significant enterohepatic recirculation (Landmesser *et al.*, 2005).

Anaesthetic Agents

These are the agents who cause reversible loss of pain and sensation. These are of two types, local anaesthetics and general anaesthetics. These agents cause hepatocellular damage (Direct toxicity and immune mediated hypersensitivity) and interfere with bilirubin metabolism and cause cholestasis (Brody and Sweet, 1963).

Halothane

Halothane was introduced into use as an anesthetic in 1956, and replaced ether as the anesthetic of choice. Within two years, isolated case reports of severe hepatitis were being reported (Brody and Sweet, 1963). Two types of halothane-mediated hepatotoxicity have been defined: The first type, type I, is a mild, self-limited postoperative hepatotoxicity, with a mild form of hepatocellular injury that can be observed in about 20% of halothane-treated patients. The mild hepatic injury is assumed to result from the direct action of halothane on the liver cells. Two clinically detectable factors appear to contribute to the mild form of hepatic injury. The first is a transient elevation of liver enzymes and the second is alteration of cellular integrity, which can be detected by electron microscopy. Lesions result from intracellular degradation of halothane via its anaerobic and aerobic pathways in combination with local hypoxia caused by an alteration of the hepatic oxygen demand and supply relationship (Conzen, 1993). The second type of halothane-mediated hepatotoxicity is type II-halothane hepatitis. The incidence of this type of hepatotoxicity after halothane administration is one case per 10000-30000 adult patients. The probable mechanism is most likely an immune-mediated hepatotoxicity; antibodies are against modified liver microsomal proteins on hepatocyte surfaces (Fallahian, 2009). There is strong evidence that the fulminant form of halothane hepatitis is mediated by the patient's own immune system. Besides signs of mild cellular injury, tissue acetylation is usually found due to the generation of reactive intermediates from halothane metabolism (Satoh *et al.*, 1985). The acetylation of intracellular proteins is considered as the first step in the pathogenesis of the severe type of hepatic injury. The second step then involves the formation of antibodies directed towards these acetylated neo-antigens. Cytochrome P450 2E1 (CYP2E1) is a major catalyst in the formation of trifluoro acetylated proteins, which have been implicated as target antigens in the mechanism of halothane hepatitis (Elisson, 1996; Reichle and Conzen, 2003).

Chloroform

Chloroform has toxic effects similar to those of carbon tetrachloride. Metabolism by microsomal cytochrome P450 is obligatory for the chloroform induced hepatic, renal and nasal toxicity. It seems that the cytochrome P450-mediated oxidative metabolism of chloroform results in the formation of inorganic chloride (excreted in the urine), CO_2 (exhaled), phosgene, and some hepatic covalently bound carbon (either via free radical or phosgene formation). Extensive covalent binding to the kidney and

liver protein has been found in direct relationship with the extant of hepatic centrilobular and renal piroximal tubular necrosis (Njoku *et al*., 1997).

Isoflurane, Enflurane, Desflurane

Postoperative hepatic injury has been reported after anaesthesia with isoflurane, enflurane and desflurane. Hepatotoxicity results from an immune response directed against hepatic proteins altered by trifluoroacetyl or trifluoroacetyl-like metabolites of the anesthetics. Only a few cases of hepatotoxicity causally related with isoflurane have been reported, a finding consistent with its lower metabolism and lower levels of formed trifluoroacetyl proteins (Sipes and Brown, 1976). Isoflurane, enflurane and desflurane undergo oxidative metabolism catalyzed by hepatic cytochrome P450 2EI. Reductive metabolites produced under hypoxic conditions produced centrilobular necrosis in the liver of rats (Ross JA et al. 1984).

Nitrous oxide

One suggestion of a facilitatory hepatotoxic role and nitrous oxide was used in virtually all cases of unexplained hepatitis (Horton *et al.*, 1994). Possible role could involve increased risk of hypoxia, and inhibition of methionine synthetase. Harmful effects of enhanced NO production in the liver include inhibition of mitochondrial respiratory chain enzymes and gluconeogenesis (Curran *et al.*, 1990). In cultured hepatocytes, NO inhibits total protein synthesis and bile canicular contraction (Dufour *et al*., 1995).

Anti-Rheumatic Drugs

Anti-rheumatic agents are among commonly used drugs associated with adverse hepatic reactions. Sulfasalazine and azathioprine are among the most important causes of acute hepatotoxicity. A population-based case–control study that included 1.64 million subjects found sulfasalazine and azathioprine to be among the most hepatotoxic drugs of any class, both associated with an incidence of liver injury of about 1 per 1,000 users (Abajo *et al*., 2004).

Sulfasalazine hepatotoxicity

The DMARD sulfasalazine is commonly used to treat RA and psoriatic arthritis (PsA). The estimated incidence of serious hepatotoxicity was higher (4 per 1,000 users) in a cohort of patients with inflammatory arthritis. The majority of cases occur within the first month of starting sulfasalazine therapy, and these can present either as a hepatocellular or cholestatic pattern of liver injury. About 25% of patients are jaundiced and a proportion of these rapidly develop hepatic failure (Jobanputra *et al*., 2008).

Gold-salt-induced cholestasis

In spite of an increased choice of DMARDs and the introduction of biologic therapies, gold salts continue to be used in 7–11% of patients with RA and PsA. Hepatotoxic effects develop in about 1% of patients receiving gold-salt therapy (Helliwell and Taylor, 2008). Rapidly progressive hepatocellular patterns of DILI leading to liver failure and death or to transplantation due to hepatic necrosis have also been reported following parenteral gold therapy (Watkins *et al*., 1988).

Azathioprine hepatotoxicity

As an immunosuppressant, azathioprine is used in the treatment of a variety of inflammatory disorders including RA and PsA. Hepatotoxic effects associated with azathioprine use include acute DILI as well as vascular syndromes including nodular regenerative hyperplasia (NRH), hepatic veno-occlusive disease and peliosis hepatis. 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 (Sparrow *et al.*, 2007; Ansari *et al*., 2008).

Methotrexate hepatotoxicity

Methotrexate has been in clinical use for more than five decades. As a DMARD, methotrexate continues to be a first-line drug in the management of early and established RA; in PsA its use seems to have increased in the past decade, and has improved clinical outcomes (Chandan *et al.*, 2008). The mechanisms underlying methotrexate hepatotoxicity are unclear, although they could be related to the cellular pathway of the drug (Kremer, 2004). Methotrexate 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 within 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 RA 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 proinflammatory cytokines. The combination of these insults could contribute to the activation of hepatic stellate cells, which leads to liver fibrosis (Desouza *et al.*, 2002).

Azathioprine-related NRH (Nodular regenerative hyperplasia)

NRH is a rare condition characterized by apparent nodularity caused by variation in the size of liver cell plates; some plates are more than one cell thick, whereas others appear thinned and atrophic. NRH is caused by alterations in blood flow associated with obliterative changes within intrahepatic portal

radicals. Atrophic areas represent acini with decreased blood flow, and nodular areas represent hypertrophic response. Thioguanine, a metabolite of azathioprine, has been implicated in vascular injury associated with lying down of collagen in the space of Disse that lies between hepatocytes and sinusoidal endothelial cells. An investigation involving 65 liver transplant recipients receiving azathioprine therapy found that two patients who suffered NRH were both heterozygous for the TPMT*3A mutation in the gene that encodes thiopurine methyltransferase, which raised the possibility that variations in azathioprine metabolism might contribute to the risk of developing this drug-induced liver disease (Breen *et al.*, 2005).

TNF inhibitors induced hepatotoxicity

Elevated levels of transaminases have been described following treatment with the three most extensively studied TNF inhibitors- adalimumab, etanercept and infliximab. The overall frequency of these events depends upon the threshold used to define hepatotoxicity. In an analysis that included 6,861 patients with RA over 14,000 patient-years, enzyme levels elevated to more than twice the upper limit of normal were seen in 0.6% of anti-TNF-treated patients overall; ALT elevations of three times the upper limit of normal were seen on 39 occasions and in nine cases ALT levels were over five times the upper limit of normal (Sokolove *et al.*, 2010). Hepatic sinusoids are involved in the clearance of immune complexes via Fc receptor-mediated interactions that in turn could activate Kupffer cells to release reactive oxygen species or lead to local hepatocyte damage. Variability in the reported frequency of hepatotoxicity with anti-TNF agents could be related to the fact that monoclonal antibodies (such as infliximab and adalimumab) form immune complexes more readily than soluble receptors (such as etanercept) (Strand *et al.*, 2007).

Anti-Epileptic Drugs (AED)

Liver injury associated with antiepileptic drugs (AED) is well recognized. The frequency of the most common AED is rare but the consequences can be very serious leading to death or liver transplantation due to acute liver failure induced by these drugs. The mechanisms behind hepatotoxicity induced by AED are not clear. Reactive metabolites from AED can, in some cases, lead to direct cytotoxicity and liver cell necrosis, whereas in other cases this may lead to neoantigen formation inducing immunoallergic mechanisms (Bjornsson, 2008).

Carbamazepine (CBZ)

Carbamazepine is a widely used antiepileptic drug, and regarded as the choice of drug for the grandmal epilepsies. It leads to increase in gamma glutamyl transferase and lesser extent in alkaline phosphatase (ALP), due to its enzyme-inducing properties. CBZ may lead to cholestatic and hepatocellular injury, even granuloma formation in the liver (Mitchell *et al.*, 1988; Forbes *et al.*, 1992). The metabolism of carbamazepine is thought to play an important role in the pathogenesis of CBZ hypersensitivity and hepatotoxicity and it has been postulated that metabolites are causative agents. *In vitro* metabolism studies using enzyme inhibitors and purified enzymes have indicated that both stable epoxide formation and reactive metabolite formations are, at least in part, dependent upon CYP 3A4. *In vivo* CBZ auto-induces its own metabolism by CYP 3A4 including the formation of ring hydroxyl metabolites 2 and 3 hydroxyl CBZ which could be generated from an unstable arene oxide intermediate. The arene oxide metabolite may lead to hapten formation. Subsequent involvement of the immune system results in the tissue injury at the sites of hapten formation, including the liver (Steven Leeder and Pirmohamad, 2003).

Valproic acid (VPA)

Valproic acid is a potent antiepileptic drug and is widely used. Usually it is well tolerated, but begin elevation of any liver enzyme may occur in as many as 20% of patients. There is a hypothetical mechanism of toxicity of VPA. This hypothesis focuses on the VPA interference with the β– oxidation of the endogenous lipids. VPA forms an ester conjugate with carnitine that may lead to secondary carnitine deficiency. Several lines of indirect evidence and in vitro studies indicate that the thioester derivative of VPA and coenzyme A may exist as a metabolic intermediate in liver tissue. Depletion of coenzyme A or VPA CoA ester itself could responsible of inhibition for mitochondrial metabolism, ATP loss and leads to cell death.

Felbamate

Felbamate (FBM) is a broad-spectrum anti epileptic medication, approved for marketing in the US in 1993, which was found to be effective against both partial and generalized seizures. Felbamate (2-phenyl-1, 3-propanediol dicarbamate, FBM) can cause aplastic anemia and hepatotoxicity. The mechanism of FBM-induced toxicities is unknown; however, it has been proposed that 2-phenylpropenal, a reactive metabolite of FBM, is responsible. The pathway leading to this metabolite involves hydrolysis of FBM to 2-phenyl-1, 3-propandiol monocarbamate (MCF), oxidation to 3-carbamoyl-2-phenylpropionaldehyde (CBMA), and spontaneous loss of carbon dioxide and ammonia (Popovic *et al.*, 2004).

Phenytoin

Phenytoin hepatotoxicity is a serious idiosyncratic reaction that occurs in less than one percent of patients. The phenytion hepatotoxicity can elevate the level of aminotransferases, lactic dehydrogenase, alkaline phosphatase, bilirubin, and prothrombin time in serum. Although the exact mechanism of phenytoin hepatotoxicity is unknown; the majority of literature supports a hypersensitivity mechanism (Smythe and Umstead, 1989).

Neuroleptic Drugs or Ant-Psychotic Drugs

Hepatotoxicity of psychotropic drugs occurs in variable but small proportion of users and therefore can be considered

unpredictable or idiosyncratic. Asymptomatic mild transient and reversible elevations of liver enzymes occur infrequently with both first and second generation antipsychotic drugs. These abnormalities occur during the first three months of treatment (Jeffrey and Allan, 2006).

Chlorpromazine (CPZ)

Chlorpromazine has been the most extensively studied. The clinical features appear to be accounted for by a mix of hypersensitivity reaction and metabolite toxicity**.** Chlorpromazine was recognized to produce jaundice. Chlorpromazine is the most extensive studied neuroleptic and the type of hepatic injury that CPZ produce is the prototype of the hepatocellular cholestasis. The mechanism of phenothiazines-induced cholestatic disease remains uncertain (Zimmerman, 1999; Ishak and Irey, 1972)

Haloperidol

Haloperidol, while structurally similar to phenothiazines, is a very rare cause of overt liver disease. The features resemble phenothiazines-induced cholestatic injury. Chlorpromazine and Haloperidol have an identical heptanoic acid side chain and, rarely, have been associated with microvesicular steatosis (Bricquir *et al.,* 1994).The side chain is metabolized by b-oxidation leading to inhibition of medium- and short-chain fatty acid β-oxidation. Thus, both drugs are converted by P450 to reactive metabolites that can induce a hypersensitivity reaction in genetically susceptible individuals (Fromenty *et al.,* 1989).

Risperidone and Quetiapine

Risperidone and quetiapine are two of the most commonly used atypical antipsychotic agents. Drug-induced cholestasis is the blockage of the flow of bile from the liver caused by a drug. This can occur by the agent selectively blocking uptake of bile components, interfering with the canalicular excretions of bile, or destroying components necessary for bile flow. Oftentimes, ALT and AST levels are normal or only mildly elevated in cholestatic injury (Mohi-ud-din and Lewis, 2004).

Olanzapine

There are reports of transient liver biochemistry abnormalities associated with olanzapine but the mechanism underlying this complication is not known. There is a case report of young man who developed transient severe abnormal liver biochemistry with hepatosplenomegaly and cholestatic jaundice, after receiving olanzapine (Lui *et al.,* 2008).

Clozapine

Clozapine is an atypical neuroleptic; an increase in alanine transaminase (ALT), which was mild and transient, occurred in 37% of recipients. The possible mechanism of hepatotoxicity is still unclear (Hummer *et al.,* 1997).

Anti-Depressants

Most tricyclic antidepressants are potentially hepatotoxic. Although other tricyclics (including amitriptyline, desipramine, doxepin) rarely cause liver disease the reported cross-reactivity should preclude their use when sensitivity to one has been suspected.

Amineptine

Amineptine-induced liver disease is mainly cholestatic, although moderate necrosis may be seen. The compound has a heptanoic acid side chain. The side chain is metabolized by β-oxidation, leading to inhibition of medium- and short-chain fatty acid b-oxidation. Thus, both drugs are converted by P450 to reactive metabolites that can induce a hypersensitivity reaction in genetically susceptible individuals (Fromenty *et al.,* 1989).

Imipramine

Imipramine can induce a cholestatic jaundice that generally is not progressive (Horst *et al.,* 1980)

MAO inhibitors

MAO inhibitors, which derive from hydrazine, are all potential hepatotoxins. Hydrazines can be metabolized by P450 to toxic intermediates. Their metabolism and mechanism resemble that of isoniazid, also a hydrazine. One substituted hydrazine MAO inhibitor remains available, namely phenelzine; there have been case reports of hepatitis (Bonkovsky *et al.,* 1986).

Acetylcholinesterase Inhibitors

Tacrine is a reversible cholinesterase inhibitor used for Alzheimer's disease. Remarkably, in about 50% of recipients, the ALT exceeds the upper limit of normal; in 25%, the value is more than three times the upper limit, and in 2%, it is20-fold increased (Selim and Kaplowitz, 2003).

The mechanism of toxicity is based on the inhibition by tacrine of acetyl cholinesterase, leading to a cholinergic coeliac ganglion-induced stimulation of an afferent sympathetic pathway, resulting in vasoconstriction, leading to impaired perfusion of the sinusoids and reperfusion injury mediated by reactive oxygen metabolites. These are not mutually exclusive hypotheses in that the former mechanism may sensitize to the latter. Thus, tacrine undergoes high extraction, suggesting that periportal hepatocytes may take up a large proportion of the drug; the uncoupling effect would increase respiration and O_2 consumption in periportal hepatocytes, thus limiting O_2 availability in the more distally perfused perivenular cells; superimposition of decreased O_2 delivery as a result of the effect on the microcirculation would further limit O_2 in the perivenular zone (Stachlewitz *et al.,* 1997).

Drugs of Abuse

Cocaine hepatotoxicity has been studied experimentally in considerable detail. Toxicity is dose-related.

Toxicity seems to depend on P450 catalyzed N-demethylation to norcocaine, which then is converted to N-hydroxynorcocaine by flavin mono-oxygenase. The latter redoxcycles to norcocaine nitroxide by receipt of an electron from NADPH, and the latter transfers electrons to O_2, generating oxidative stress (Kloss *et al*., 1984).

Anti-Hypertensive Drugs

Methyl dopa is used in the treatment of hypertension. Both minor and severe forms of liver damage have been reported in patients receiving methyl dopa. The former consists of asymptomatic, and often transient, rises of serum transaminases and according to various reports is found in two to 10 % of patients receiving the drug (Rodman *et al.*, 1976). The liver damage, which may take the form of acute hepatitis, chronic active hepatitis or cholestasis occurs more commonly in women and there is not the same close temporal relationship between the time of onset of overt clinical hepatic injury, which in 50% of cases occurs after four weeks. *In vitro* studies have shown that the drug is metabolized by both human and rat liver microsomes, by the cytochrome P450 system, with consequent covalent binding to cellular macromolecules (Leonard SW *et al.*, 1965). This covalent binding is inhibited by a variety of agents, including glutathione, ascorbic acid and superoxide dismutase consistent with the oxidation of methyl dopa by cytochrome P450-generated superoxide anions to a reactive quinone or semi-quinone (Dybing, 1977).

Other Drugs

Few other drugs also reported to cause hepatotoxicity are Glucocorticoids, Antibiotics (Amoxicillin, Ciprofloxacin, Erythromycin), Oral contraceptives and antifungals (Fluconazole, itraconazole).

CONCLUSION

The list of hepatotoxic drugs is huge and a complete coverage is difficult. To sum up thus there are a large category of drugs used for different therapeutic indications which are toxic to the liver and thus should be cautiously administered; particularly when given at high doses or used for chronic or long term administration.

ACKNOWLEDGEMENT

The authors would like to thank The Director, Rayat Institute of Pharmacy, Railmajra (Punjab) for providing the necessary facilities for the research work.

REFERENCES

Abajo F.J., Montero D., Madurga M., Garcia Rodriguez L.A. Acute and clinically relevant drug-induced liver injury: a population based case–control study. Br J Clin Pharmacol. 2004; 58: 71–80.

Aceti A., Pasquazzi C., Zechini B., De Bac C. Hepatotoxicity development during antiretroviral therapy containing protease inhibitors in patients with HIV. The role of hepatitis B and C virus infection. J Acquir Immune Defic Syndr. 2002; 29: 41–48.

Aithal G.P. Diclofenac-induced liver injury: a paradigm of idiosyncratic drug toxicity. Expert Opin Drug Saf. 2004; 3: 519–523.

Aithal G.P. Hepatotoxicity related to antirheumatic drugs. Nat Rev Rheumatol. 2011; 7: 139-150.

Alonso J.J., Osorio J.M., Cabello F.G., Osa A.L., Leon L., Garcia J.D.M. Atorvastatin induced cholestatic hepatitis in a young woman with systemic lupus erythematosus. Arch Intern Med. 1999; 159: 1811–1812.

Ansari A., Elliott T., Baburajan B., Mayhead P., Donohue J.O., Anderson J.S., Dudley J. Long-term outcome of using allopurinol co-therapy as a strategy for overcoming thiopurine hepatotoxicity in treating inflammatory bowel disease. Aliment Pharmacol Ther. 2008; 28: 734-741.

Basseri S., Austin R.C. ER stress and lipogenesis: a slippery slope toward hepatic steatosis. Dev Cell. 2008; 15: 795-796.

Benichou C. Criteria of drug-induced liver disorders. Report of an International Consensus Meeting. J Hepatol. 1990; 11: 272-276.

Bertolami M.C. Mechanisms of hepatotoxicity. Arq Bras de Cardiol. 2005; 85(5): 25-27.

Bissell D., Gores G., Laskin D., Hoofnagle J.H. Drug-induced liver injury: mechanisms and test systems. Hepatol. 2001; **33:** 1009–1013.

Bissuel F., Bruneel F., Habersetzer F., Chassar D., Cotte L., Chevallier M., Bernuau M., Lucet J.C., Trepo C. Fulminant hepatitis with severe lactate acidosis in HIV-infected patients on didanosine therapy. J Intern Med. 1994; **235:** 367–371.

Bjornsson E. Hepatotoxicity associated with antiepileptic drugs. Acta Neurol Scand. 2008; 118: 281–290.

Bolder U., Trang N.V., Hagey L.R., Schteingart C.D., Ton-Nu H.T., Cerre C. Sulindac is excreted into bile by a canalicular bile salt pump and undergoes a cholehepatic circulation in rats. Gastroenterol. 1999; 117: 962–971.

Bonfanti P., Landonio S., Ricci E., Artinelli C., Fortuna *P.*, Faggion I., Quirino T. Risk factors for hepatotoxicity in patients treated with highly active antiretroviral therapy. J Acquir Immune Defic Syndr. 2001; 27: 316–318.

Bonkovsky H., Blanchette P., Schned A. Severe liver injury due to phenelzine with unique hepatic deposition of extracellular material. Am J Med. 1986; 80: 689-692.

Bort R., Ponsoda X., Jover R., Gomez-Lechon M.J., Castell J.V. *Diclofenac toxicity to hepatocytes: a role for drug metabolism in cell toxicity*. J Pharmacol Exp Ther. 1999*;* 288*:* 65–*72.*

Breen D.P., Marinaki A.M., Arenas M., Hayes P.C. Pharmacogenetic association with adverse drug reactions to azathioprine immunosuppressive therapy following liver transplantation. Liver Transpl. 2005: 11: 826–833.

Bricquir Y., Larrey D., Blanc P., Pageaux G.P., Michel H. Tianeptine-an instance of drug-induced hepatotoxicity predicted by prospective experimental studies. J Hepatol. 1994; 21: 771-773.

Brinkman K., Hofstede K., Burger D., Smeitink J., Koopmans P. Adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as common pathway. AIDS. 1998; 12: 1735–1744.

Brody G.L., Sweet R.B. Halothane anesthesia as a possible cause of massive hepatic necrosis. Anesthesiol. 1963; 24: 29-37.

Conzen P. Effect of inhalational anesthetics on the liver. Baillierere's Best Practice & Research Clinical Anesthesiology. 1993; 4: 1015-1034.

Caldwell S.H., Hespenheide E.E., Borstel R.W. Myositis, microvesicular hepatitis, and progression to cirrhosis from troglitazone added to simvastatin. Digest Dis Sci. 2001; 46: 376.

Carbonero L., Nunez M., Soriano V. Incidence of liver injury after beginning antiretroviral therapy with efavirenz or nevirapine. HIV Clin Trials. 2003; 4: 115–120.

Chandran V., Schentag C.T., Gladman D.D. Reappraisal of the effectiveness of methotrexate in psoriatic arthritis: results from a longitudinal observational cohort. J Rheumatol. 2008; 35: 469–471.

Chen H., Huang C.Y., Wilson M.W., Lay L.T., Robertson L.W., Chow C.K., Glauert H.P. Effect of the peroxisome proliferators ciprofibrate and perfluorodecanoic acid on hepatic cell proliferation and toxicity in Sprague-Dawley rats. Carcinogenesis. 1994; 15: 2847–2850.

Chitturi S., George J. Hepatotoxicity of commonly used drugs: nonsteroidal anti-inflammatory drugs, antihypertensives, antidiabetic agents, anticonvulsants, lipid lowering agents, psychotropic drugs. Semin Liver Dis. 2002; 22: 169–183.

Cohen D.E., Anania F.A., Chalasani N. National Lipid Association Statin Safety Task Force Liver Expert Panel. An assessment of statin safety by hepatologists. Am J Cardiol. 2006; 97: 77–81.

Connor N.O., Dargan P.I., Jones A.L. Hepatocellular damage from non-steroidal anti-inflammatory drugs. QJM: An International Journal of Medicine. 2003; 96: 787-791.

Cooper C., Parbhakar M., Angel J. Hepatotoxicity associated with antiretroviral therapy containing dual versus single protease inhibitors in individuals co infected with hepatitis C virus and HIV. Clin Infect Dis. 2002; 34: 1259–1263.

Curran R.D., Billiar T.R., Stuehr D.J., Ochoa J.B., Harbrechet B.G., Flint S.G. Multiple cytokines are required to induce hepatocyte nitric oxide production and inhibit total protein synthesis. Ann Surg. 1990; 212: 462-471.

Dalton T.A., Berry R.S. Hepatotoxicity associated with sustained-release niacin. Am J Med. 1992; 93(1): 102–104.

Desouza C., Keebler M., Namara D.B., Fonseca V. Drugs affecting homocysteine metabolism: impact on cardiovascular risk. Drugs. 2002; 62: 605–616.

Desta Z., Soukhova N.V., Flockhart D.A. Inhibition of cytochrome P450 (CYP450) isoforms by isoniazid: potent inhibition of CYP2C19 and CYP3A. Antimicrob Agents Chemother. 2001; 45: 382–392.

Dix K.J., Coleman D.P., Jeffcoat A.R. Comparative metabolism and disposition of gemfibrozil in male and female Sprague-Dawley rats and Syrian golden hamsters. Drug Metab Dispos. 1999; 27: 138–146.

Dufour J.F.J., Turner T.J., Arias I.M. Nitric oxide blocks bile canalicular contraction by inhibiting inositol triphosphate-dependent calcium mobilization. Gastroenterol. 1995; 108: 841-849.

Dybing E. Activation of methyl dopa, paracetamol and frusemide by human liver microsomes. Acta Pharmacol Toxicol. 1977; 41: 89-93.

Elisson E., Kenna J.G. Cytochrome P4502E1 is a cell surface auto antigen in halothane hepatitis. Mol Pharmacol. 1996; 50: 573-582.

Etchason J.A., Miller T.D., Squires R.W., Allison T.G., Gau G.T., Marttila J.K. Niacin-induced hepatitis: a potential side effect with low-dose time-release niacin. Mayo Clin Proceed. 1991; 66: 23–28.

Fallahian F. Halothane Induced Hepatitis. Shiraz e-medical Journal. 2009; 10: 209–220.

Forbes G.M., Jeffrey G.P., Shilkin K.B., Reed W.D. Carbamazepine hepatotoxicity: Another case of the vanishing bile duct syndrome. Gastroenterol. 1992; 102: 1385-1388.

Fromenty B., Freneaux E., Labbe G., Deschamps D., Larrey D., Letteron P., Pessayre D. Tianeptine, a new tricyclic antidepressant metabolized by β-oxidation of its heptanoic side chain, inhibits the mitochondrial oxidation of medium and short chain fatty acids in mice. Biochem Pharmacol. 1989; 38: 3743-3751.

Girling D.J. The hepatic toxicity of antituberculosis regimens containing isoniazid, rifampicin and pyrazinamide. Tubercle. 1978; 59: 13–32.

Gisolf E., Dreezen C., Danner, Weel J.L., Weverling G.J. Risk factors for hepatotoxicity in HIV-1 infected patients receiving ritonavir and saquinavir with or without stavudine. Clin Infect Dis. 2000; **3**: 1234–1239.

Grimbert S., Pessayre D., Degott C., Benhamou J.P. Acute hepatitis induced by HMG-CoA reductase inhibitor, lovastatin. Digest Dis Sci. 1994; 39: 2032–2033.

Helliwell P.S., Taylor W.J. Treatment of psoriatic arthritis and rheumatoid arthritis with disease modifying drugs- comparison of drugs and adverse reactions. J Rheumatol. 2008; 35: 472–476.

Hodis H.N. Acute hepatic failure associated with the use of low-dose sustained-release niacin. JAMA. 1990; 264: 181.

Horsmans Y., Desager J.P., Harvengt C. Biochemical changes and morphological alterations of the liver in guinea-pigs after administration of simvastatin (HMG CoA reductase-inhibitor). Pharmacol Toxicol. 1990; 67: 336–339.

Horst D., Grace N., Le Compte P. Prolonged cholestasis and progressive hepatic fibrosis following imipramine therapy. Gastroenterology. 1980; 79: 550-554.

Horton R.A., Ceppi E.D., Knowles R.G., Titheradges M.A. Inhibition of hepatic gluconeogenesis by nitric oxide: a comparison with endotoxic shock. Biochem J. 1994; 299: 735-739.

Huang Y.S., Chern H.D., Su W.J., Wu J.C., Lai S.L., Yang S.Y., Chang F.Y., Lee S.D. Cytochrome P450 2E1genotype and the susceptibility to antituberculosis drug-induced hepatitis. Hepatology 2003; 37: 924–930.

Hummer M., Kury M., Kurzthaler I., Oberbauer H., Miller C., Fleischhacker W. Hepatotoxicity of clozapine. J Clin Psychopharm. 1997; 17: 314-317.

Ishak K., Irey N. Hepatic injury associated with the phenothiazines. Arch Path. 1972; 93: 283-304.

Jacobson T.A. Statin safety: lessons from new drug applications for marketed statins. Am J Cardiol. 2006; 97: 44–51

Jeffrey LA and Allan T. Handbook of Psychiatric Drugs. John Wiley and Sons Ltd., Chichester UK (2006) 34.

Jenner A.M., Timbrell J.A. *In vitro* microsomal metabolism of hydrazine. Xenobiotica 1995; 25: 599–609.

Jenner A.M., Timbrell J.A. Influence of inducers and inhibitors of cytochrome P450 on the hepatotoxicity of hydrazine *in vivo*. Arch Toxicol. 1994; 68: 349–357.

Jobanputra P., Amarasena R., Maggs F., Jubb R., Homer D. Hepatotoxicity associated with sulfasalazine in inflammatory arthritis: a case series from a local surveillance of serious adverse events. BMC Musculoskelet Disord. 2008; 9: 48.

Johnson S., Chan J., Bennett C. Hepatotoxicity after prophylaxis with a nevirapine-containing antiretroviral regimen. Ann Intern Med. 2002; 137**: 146–**147.

Kanathur N., Mathai M.G., Byrd R.P., Fields C.L., Roy T.M. Simvastatin- Diltiazem drug interaction resulting in rhabdomyolysis and hepatitis. Tennessee Med. 2001; 94: 339–341.

Kharasch E.D., Hankins D., Mautz D., Thummel K.E. Identification of the enzyme responsible for oxidative halothane metabolism: implications for prevention of halothane hepatitis. The Lancet. 1996; 347: 1367-1371.

Kloss M.W., Rosen G.M., Rauckman E.J. Cocaine-medicated hepatotoxicity. A critical review. Biochem Pharmacol. 1984; 33: 169-173.

Kontorinis N., Dieterich D. Hepatotoxicity of antiretroviral therapy. AIDS Rev. 2003; 5: 36–43.

Kremer J.M. Toward a better understanding of methotrexate. Arthritis Rheum. 2004; 50: 1370–1382.

Landmesser U., Bahlmann F., Mueller M., Spiekermann S., Kirchhoff N., Schulz S. Simvastatin versus ezetimibe: pleiotropic and lipid lowering effects on endothelial function in humans. Circulation. 2005; 111: 2356-2363.

Leist M., Gantner F., Kunstle G., Wendel A. Cytokine-mediated hepatic apoptosis. Rev Physiol Biochem Pharmacol. 1998; **133:** 109-155.

Leonard S.W., Goffard R.W., Humphrey D.C. Treatment of hypertension with methyl dopa alone or combined with Guanethedine: A report of 63 cases. Am Heart J. 1965; 69: 610- 618.

Lewis, J.H. (2007). Nonsteroidal anti-inflammatory drugs and leukotriene receptor antagonists: pathology and clinical presentation of hepatotoxicity. In N. Kaplowitz, L.D. DeLeve (Eds.) Drug-induced liver disease. (pp. 377-390). New York: Informa Healthcare USA.

Lui S.Y., Steve T., Lam M., Cheung Eric F.C. Case Report: Possible olanzapine-induced hepatotoxicity in a young Chinese patient. Hong Kong Med J. 2009; 15: 5.

Maffei F.R., Carini M. The inhibitory effect of pyrazinamide on microsomal monooxygenase activities is related to the binding to reduced cytochrome P-450. Pharmacol Res Commun. 1980; 12: 523–537.

Martinez E., Blanco J., Arnaiz J.A., Perez-Cuevas J.B., Mocroft A., Cruceta A., Marcos M.A., Milinkovic A., Garcia-Viejo M.A., Mallolas J., Carne X., Phillips A., Gatell J.M. Hepatotoxicity in HIV-infected patients receiving nevirapine-containing antiretroviral therapy. AIDS 2001; 15: 1261–1268.

Masubuchi Y., Yamada S., Horie T. Possible mechanisms of hepatocyte injury induced by diphenylamine and its structurally related NSAIDS. J Pharmacol Exp Ther. 2000*; 292:* 982*–987.*

Mitchell J.R., Jollow D.J., Potter W.Z., Davis D.C., Gillette J.R., Brodie B.B. Acetaminophen-induced hepatic necrosis. I. Role of drug metabolism. J Pharmacol Exp Ther. 1973; 187: 185–194.

Mitchell M.C., Boitnott J.K., Arregui A., Maddrey W.C. Granulomatous hepatitis associated with carbamazepine therapy. Am J Med. 1981; 71: 733-735.

Mohi-ud-din R., Lewis J.H. Drug and chemical-induced cholestasis. Clin Liver Dis. 2004; 8: 95-132.

Nakad A., Bataille L., Hamoir V., Sempoux C., Horsman Y. Atorvastatin-induced acute hepatitis with absence of cross-toxicity with simvastatin. Lancet. 1999; 353: 1763–1764.

Nishimura Y., Kurata N., Sakurai E., Yasuhara H. Inhibitory effect of anti-tuberculosis drugs on human cytochrome P450-mediated activities. J Pharmacol Sci. 2004; 96: 293–300.

Njoku D., Laster M.J., Gong D.H. Biotransformation of halothane, enflurane, isoflurane and desflurane to trifluoroacetylated liver proteins: association between protein acylation and hepatic injury. Anest Analg. 1997; 84: 173-178.

Nunez M., Lana R., Mendoza J., Martin-Carbonero L., Eger E.I., Reed G.F., Martin J.L. Risk factors for severe hepatic injury following the introduction of HAART. J Acquir Immune Def Syndr. 2001; **27:** 426–431.

Nunez M. Hepatotoxicity of antiretrovirals: Incidence, mechanisms and management. J Hepat. 2006; 44: 132–139.

Ostapowicz G., Fontana R.J., Schiodt F.V., Larson A., Davron J.T., Steven H.B., Timothy M., Reish J. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med. 2002; 137: 947–954.

Padma V.V., Suja V., Shyamala D.C.S., Prema. Hepatoprotective effect of Liv-52 on antitubercular drug-induced hepatotoxicity in rats. **Fitoterapia.** 1998; 69(6): 520-522.

Pai V., Koranyi K., Nahata M. Acute hepatitis and bleeding possibly induced by zidovudine and ritonavir in an infant with HIV infection. Pharmacother. 2000; 20: 1135–1140.

Palmon R., Koo B., Shoultz D., Dieterich D. Lack of hepatotoxicity associated with non nucleoside reverse transcriptase inhibitors. J Acquir Immun Defic Syndr. 2002; 29: 340-345.

Pelli N., Setti M., Ceppa P., Toncini C., Indiveri F. Autoimmune hepatitis revealed by atorvastatin. Eur J Gastroen Hepat. 2003; 15: 921-924.

Popovic M., Nierkens S., Pieters R., Uetrecht J. Investigating the role of 2-phenylpropenal in felbamate-induced idiosyncratic drug reactions**.** Chem Res Toxicol. 2004; 17: 1568-1576.

Reichle F.M., Conzen P.F. Halogenated inhalational anesthetics. Best Practice & Research Clin Anaesthesiol. 2003; 17: 29-46.

Reimund E., Ramos A. Niacin-induced hepatitis and thrombocytopenia after 10 years of niacin use. J Clin Gastroenterol. 1994; 18: 270–271.

Ricaurte B., Guirguis A., Taylor H.C., Zabriskie D. Simvastatin-amiodarone interaction resulting in rhabdomyolysis, azotemia, and possible hepatotoxicity. Annals of Pharmacotherapy. 2006; 40(4): 753–757.

Rodman J.S., Deutsch D.J., Gutman S.I. Methyl dopa hepatitis. A report of six cases and a review of the literature. Am J Med. 1976; 60: 941-948.

Ross J.A., Monk S.J., Duffy S.W. Effect of Nitrous Oxide on halothane induced hepatotoxicity in hypoxic enzyme induced rats. Br J Anaest. 1984; 56: 527-533.

Satoh H., Fukuda Y., Anderson D.K. Immunological studies on the mechanism of halothane induced hepatotoxicity: immunohistochemical evidence of trifluoro-acetylated hepatocytes. J Pharmacol Exp Ther. 1985; 223: 857-862.

Selim K., Kaplowitz N. Hepatotoxicity of Psychotropic Drugs. Hepatology. 2003; 29: 1348-1350.

Sgro C., Clinard F., Ouazir K., Chanay H., Allard C., Guilleminet C., Lenoir C., Lemoine A., Hillon P. Incidence of drug-induced hepatic injuries: A french population-based study. Hepatology. 2002; 36: 451–455.

Sharma A., Chakraborti K.K., Handa S.S. Anti-hepatotoxic activity of some Indian herbal formulations as compared to silymarin. Fitoterapia. 1991; 62: 229-235.

Sipes I.G., Brown B.R. An animal model of hepatotoxicity associated with halothane anesthesia. Anesthesiology. 1976; 45: 622-628.

Smythe M.A., Umstead J.S. Phenytoin hepatotoxicity: a review of the literature. Ann Pharmacotherapy. 1989; 23: 13-18.

Sokolove J., Greenberg D.J., Strand V., Curtis J.R., Kavanaugh A., Kremer J., Anofrei A., Reed G., Calabrese L., Hooper M. Risk of elevated liver enzymes associated with TNF inhibitor utilisation in patients with rheumatoid arthritis. Ann Rheum Dis. 2010; 69: 1612–1617.

Sparrow M.P., Hande S.A., Friedman S., Cao D., Hanauer S.B. Effect of allopurinol on clinical outcomes in inflammatory bowel disease nonresponders to azathioprine or 6-mercaptopurine. Clin Gastroenterol Hepatol. 2007; 5: 209–214.

Stachlewitz R., Arteel G., Raleigh J., Connor H., Mason R., Thurman R. Development and characterization of a new model of tacrine-induced hepatotoxicity: role of the sympathetic nervous system and hypoxia-reoxygenation. J Pharmacol Exp Ther. 1997; 282: 1591-1599.

Steven Leeder J., Pirmohamad M. Drug induced liver Diseases. United States of America: Informa Healthcare Publishers. Chapter 18, Anticonvulsant Agents; p. 425-436.

Strand V., Kimberly R., Isaacs J.D. Biologic therapies in rheumatology: lessons learned future directions. Nat Rev Drug Discov.2007; 6: 75–92.

Subramonium A., Pushpangadan P. Development of Phytomedicines for liver diseases. Indian J Pharmacology. 1999; 31: 166-175.

Sulkowski M., Thomas D., Chaisson R., Moore R. Hepatotoxicity associated with antiretroviral therapy in adults infected with HIV and the role of hepatitis C or B virus infection. J Am Med Assoc. 2000; 283: 74–80.

Sulkowski M., Thomas D., Mehta S., Chaisson, Moore R. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. Hepatology. 2002; 35: 182–189.

Sulkowski M. Hepatotoxicity associated with antiretroviral therapy containing HIV-1 protease inhibitors. Semin Liver Dis. 2003; 23: 183–194.

Tarazi E.M., Harter J.G., Zimmerman H.J., Ishak K.G., .Eaton RA. Sulindac-associated hepatic injury: analysis of 91 cases reported to the Food and Drug Administration. Gastroenterology. 1993; 104: 569–574.

Tostmann A., Boeree M.J., Aarnoutse R.E., Lange W.C.M., Vander Ven A.J., Dekhuijzen R. Anti-tuberculosis drug-induced hepatotoxicity: Concise up-to-date review. J Gastroenterol Hepatol. 2008; 23: 192-202.

Walker A.M. Quantitative studies of the risk of serious hepatic injury in persons using nonsteroidal anti-inflammatory drugs. Arthritis Rheum. 1997; 40: 201–208.

Walker U., Setzer B., Venhoff N. Increased long-term mitochondrial toxicity in combinations of nucleoside analogue reverse-transcriptase inhibitors. AIDS. 2002; **16:** 2165–2173.

Watkins P.B., Schade R., Mills A.S., Carithers R.L., Thiel D.H. Fatal hepatic necrosis associated with parenteral gold therapy. Dig Dis Sci. 1988; 33: 1025–1029.

Wen X., Wang J.S., Neuvonen P.J., Backman J.T. Isoniazid is a mechanism-based inhibitor of cytochrome P450 1A2, 2A6, 2C19 and 3A4 isoforms in human liver microsomes. Eur J Clin Pharmacol. 2002; 57: 799–804.

Wit F., Weverling G., Weel J., Jurrians S., Lange J. Incidence and risk factors for severe hepatotoxicity associated with antiretroviral combination therapy. J Infect Dis .2002; 186: 23–31.

Zimmerman H.J. Update on hepatotoxicity due to classes of drugs in common clinical use: non-steroidal drugs, anti-inflammatory drugs, antibiotics, anti-hypertensives and cardiac and psychotropic agents. Semin Liver Dis. 1990; 10: 322–338.

Zimmerman H.J. Hepatotoxicity: The adverse effects of drugs and other chemicals on the liver. 2nd ed. Lippincott Williams and Wilkins, Philadelphia (1999) 483-498.