Drug and Herb induced liver injury: a short review

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ABSTRACT

Chemical induced liver injury is a pathological condition caused by diver's medications and other xenobiotics, leading to deficiencies in liver functions with the elimination of other diagnosis. Liver injury is prevalent in the world and can result in serious clinical outcome and has possibly fatal outcome. Chemical induced liver injury has an estimated annual incidence 10-15 per 10,000-100,000 patients received several prescription medications. The kind of liver injury are almost 10% cases with acute hepatitis, and is the most common cause of acute liver failure in the United States. Also, liver injury appeared after approval for marketing has restricted the use of many drugs (e.g., isoniazid, labetalol, and felbamate). Therefore, especially drug-induced liver injury is currently the major reason for discontinuation of a new compound in development or for withdrawal of a successfully launched drug from the market. In this review, we researched that mechanisms of liver injury with drugs and herbal preparations, and potential risks have been reported.

Keywords: Liver injury, hepatotoxicity, drug withdrawal

INTRODUCTION

Chemical induced liver injury is a pathological condition caused by several drugs, herbal and dietary supplements, and other xenobiotics, leading to deficiencies in liver functions after the elimination of other diagnosis (Suk and Kim 2012). Drug-induced liver injury is rare; however, is one of the commonest causes of failed drug approval from regulatory authorities, adverse drug reactions, withdrawal of medications from the market and acute liver failure. As it is well known, pharmaceutical preparations contains drugs approved by regulative authorities, and they still are often the main cause of the adverse liver reactions (Clinical 2009; Temple 2006).

Several retrospective and prospective studies have been reported the incidence and risk factors for chemical-induced liver injury in the medical literatures. In the world, the estimated annual incidence rate of liver injury is 13.9-24.0 per 100,000 people (Oh et al. 2015; Suk and Kim 2012). The annual incidence rate of liver injury has varied from 1.27 to 14 cases per 10^5 inhabitants in reported studies from Europe (Dağ et al 2014; Hussaini and Farrington 2014; Sgro et al. 2002). In the United States, drugs are related to over 50% of acute liver failure cases that circa 2000 annually reported (Korth 2014). Available data from Turkey about chemical-induced liver injury are very limited. Published data about liver injury from our country consist of case reports and experimental studies. In a large retrospective analysis from Ankara, antibiotics were the most common causative agents in 84 of 170 patients with drug-induced liver injury (Dağ et al. 2014).

THE ETIOLOGY OF LIVER INJURY

Most researchers agree that the etiology of liver injury can be commonly separated into two categories. Firstly, a cause of direct hepatotoxicity or liver injury is the drug itself or its metabolite as is the case with acetaminophen overdose. Several other drugs

can cause dose-related hepatotoxicity as in bromfenac, cyclophosphamide, methotrexate *etc*. Second category is commonly described as idiosyncratic. A majority of liver injury cases arise from idiosyncratic metabolic responses or unexpected medication reactions, and the pathogenesis of reactions is uncertain (Njoku 2014; Suk and Kim 2012).

Biotransformation takes important stage in the development of chemical induced liver injury through the formation of directly toxic or reactive metabolites (Figure 1). The metabolites could effectuate direct injury to the hepatocyte by interaction with important cellular functions. For example; bioactivation of acetaminophen by CYP2E1 leads to the formation of the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI). The metabolite has an affinity to intracellular organelles including the mitochondria. Further information about mechanism could be achieved by the sources (Njoku 2014). Direct toxic or reactive metabolites could also raise sensitization of hepatocytes to cytokine-induced damage such as in bacterial endotoxins represented by lipopolysaccharide via TNF-α, in some cases, from sensitization to injury in liver (Njoku 2014). In third way, drug and reactive metabolites process through haptenization including covalent conversion of native cellular proteins, which subsequently altered and organize immune recognition. In a susceptible host, the last process initiates a cascade of cytokine driven immune reactions be the result of hepatotoxicity (Njoku 2014; Garcia-Cortes et al. 2011).

RISK FACTORS FOR LIVER INJURY

Up to present many studies with liver injury and its risk factors are poorly understood. The susceptibility to chemical-induced liver injury is dependent on aging and gender, genetic factors, pre-existing liver disease, oxidative and mitochondrial damage, and social factors (Boelsterli and Lim 2007; Chen et al. 2015; Gómez-Lechón et al. 2015; Hussaini and Farrington 2014).

Aging: Decreased in renal function and reduced conjugation reactions in hepatic metabolism by age affects drugs pharmacokinetics. The general hypothesis suggested that older age probably increases chemical-induced liver injury susceptibility. In the Spanish Drug-Induced Liver Injury Registry, 46% of patients with liver injury were ≥60 years of age. United States Drug-Induced Liver Injury Network (DILIN) reported 18.5% of patients with liver injury to be 65 years or older (Chen et al. 2015). Liver injury is rare in children, which are related with the accidental exposure and overdose (Korth, 2014). In Korea, the age distribution was varied with the age groups <20, 20-29, 30-39, 40-49, 50-59, and ≥60 representing 1.3, 8.1, 16.4, 27.5,
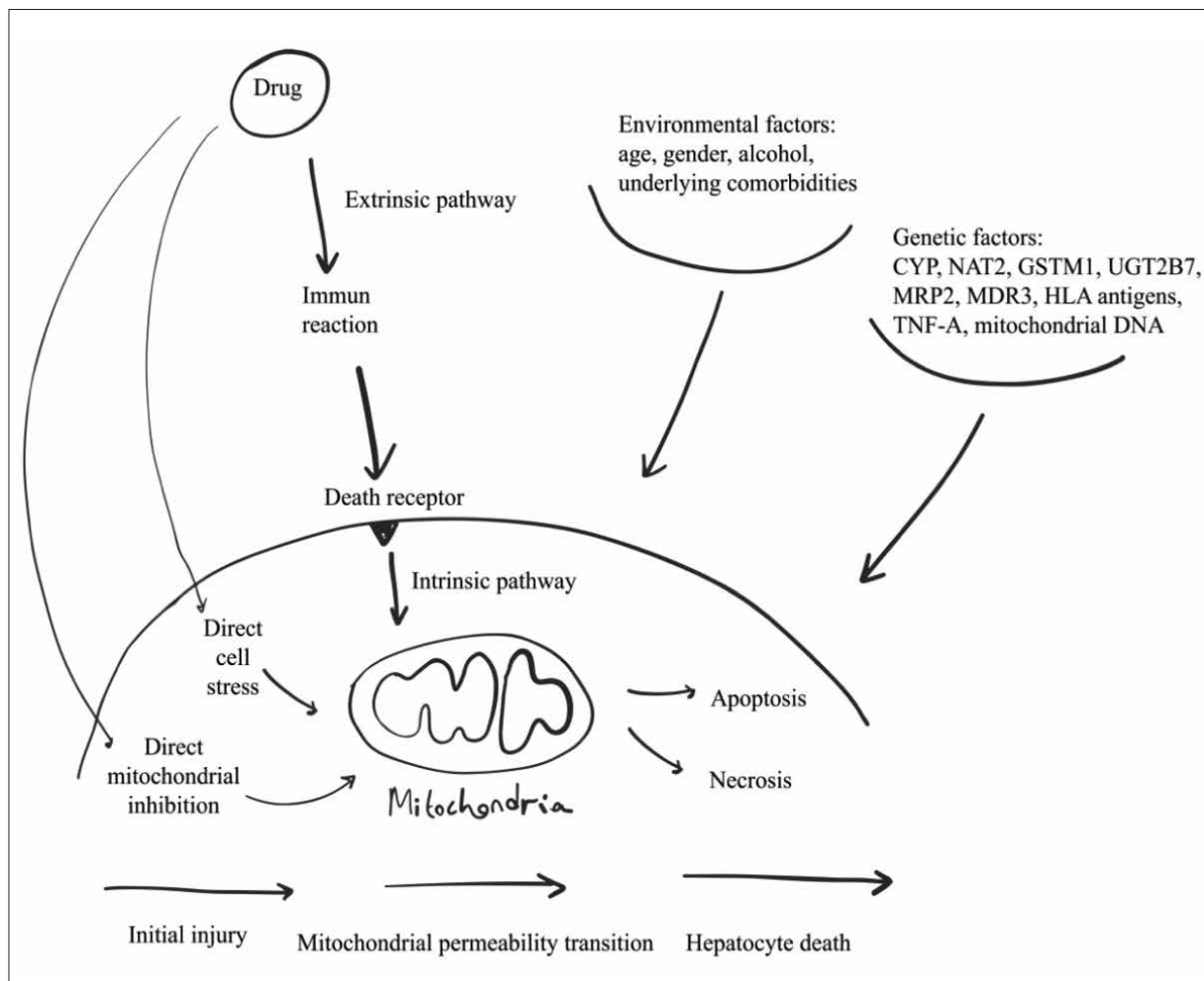
Figure 1. Three possible ways in the development of DILI (The figure was modified by Suk and Kim 2012)

21.8, and 24.8% of cases, respectively. There was no significant difference between age groups (Suk and Kim 2012).

Gender: Pubertal development, sex hormones, pregnancy and growth hormone levels also affects drug metabolizing enzymes. In males CYP3A4, one of the main drug metabolizing enzymes, has a higher expression rate related to clearance ,of acetaminophen in comparison with females (Chen et al. 2015). In a retrospective study of the United Network for Organ Sharing (UNOS) conducted in 1990-2002 by Russo et al. (2004), it was reported 270 patients with liver transplantation possessed drug-induced liver injury, and it was observed 76% of recipients were female (Hussaini and Farrington 2014). The DILIN network reported that the incidence in women of drug-induced liver injury was 65%, significantly greater than a rate of 35% in men (Chalasani et al. 2008). An another liver injury model showed that severe hepatitis and antibody production in females are more than in males with the higher level of pro-inflammatory hepatic cytokines. In halothane-induced liver injury, estrogens reduced liver injury in mice while progesterone aggravated the damage possibly by inducing inflammation and immune response (Chen et al. 2015).

Genetics: There is limited research about the issue in literature. However, genetics could be an important factor in the susceptibility to liver injury. Some drug metabolizing genes coding for CYPs, N-acetyltransferase (NAT), glutathione-S-transferase (GST) have been associated with racial differences in liver injury caused by anti-tuberculosis, non-steroidal anti-inflammation and antibacterial drugs. Patients with variations in these genes have an increased risk of developing liver injury (Stepan et al. 2011; Chen et al. 2015). CYP2E1*1A variant has been associated with the generation of a toxic metabolite of anti-tuberculosis drugs, also improving of reactive oxygen species. CYP2C8 has been related with liver injury following the generation of toxic metabolites of diclofenac (Njoku 2014). For diclofenac, several possible reactive intermediates have been postulated, including the 2,5- and 2,4'-quinone imines and both the parent and 4'-hydroxy-diclofenac acyl-glucuronides. This metabolites may result from combined metabolism involving CYP2C8 and uridine-5'-diphosphate glucuronosyl tranferase (UGT) 2B7, and, in fact, the CYP2C8*4 and UGT2B7*2 variants were found to be associated with diclofenac induced liver injury (Stepan et al. 2011; Njoku 2014). Isoniazid has two reactive metabolites, which are acetylhydrazine and hydrazine. The metabolites are known to be hepatotoxic and metabolized by NAT-2. In addition to detoxification by NAT-2, GST has a key role in neutralization of reactive oxygen species and in detoxification of reactive metabolites from isoniazid (Njoku 2014).

It was found out that human leukocyte antigen (HLA) variants are related with each other on the subject of hepatotoxicity. The relation between the mechanism of liver injury and HLA is still unclear. Genome-Wide Association (GWA) studies have assembled a wide variety of genetic markers in the major histocompatibility complex (MHC) region. The strongest associations have been found with especially HLA class I and II genes. However, there is no found direct evidence. So, the gene products are causal although the main drug or metabolite either

might interact direct with specific HLA class I or II proteins in an antigen presentation reaction to T cells or might produce a covalent complex with intracellular proteins (Daly 2012). It was declared person with HLA-DRB1*1501-DRB5,*0101-DQB1*0602 haplotype had almost more than 10 times risk in developing hepatotoxicity following amoxicillin clavulanate with GWAS (Njoku 2014). The whole HLA association for lumiracoxib-related liver injury was less strong than that for flucloxacillin-related liver injury. Clinicians should avoid typing the prescription including lumiracoxib to the 34% of Europeans positive to a HLA allele (DQA1*0102) in linkage disequilibrium with DRB1*1501 (Daly 2012). HLA-DRB1*1501-DQB1*0602-DQA1*0102 haplotype have been detected for both amoxicillin-clavulanate and lumiracoxib-related liver injury. The association between HLA-B*5701 and flucloxacillin related liver injury is observed in abacavir-induced hypersensitivity reactions that ordinarily have not affect on the liver, but the positive predictive value for HLA-B*5701 in abacavir hypersensitivity is substantially higher than that for flucloxacillin-related liver injury (Daly 2012).

Pre-existing Liver Disease: The presence of fatty liver disease or chronic viral hepatitis might increase the risk of chemical-induced liver injury. Compared to a normal liver, the fatty liver is more susceptible to oxidative stress, endotoxin, cytokine-mediated injury and ischemia (Hussaini and Farrington 2014). Immune renewal from human immunodeficiency virus (HIV) treatment might aggravate the liver injury of pre-existing hepatitis C virus (HCV) viral hepatitis causing immune mediated liver injury (Kramer et al. 2005). Alternatively, the mitochondrial toxicity associated with antiretroviral therapy can produce hepatic steatosis, which raise fulminant hepatic failure (Spengler et al. 2002). Furthermore, HCV may increase mitochondrial toxicity by impairing mitochondrial DNA (mtDNA) (Spengler et al. 2002).

Oxidative and Mitochondrial Damage: Oxidative stress could be occurred following drug metabolism or directly be generated in mitochondria subsequently leading to inflammatory cell response by damage hepatocytes, which cause oxidative damage in the liver. When drugs taken, disable respiratory-chain enzymes or DNA, oxidative stress results with subsequent anaerobic metabolism, lactic acidosis, and triglyceride accumulation (Lee, 2003). Cellular and mitochondrial damage could induce activation of diverse signal transduction pathways regulating cell death and survival. The c-Jun kinase (JNK) signalling pathway is a significant cellular stress component leading activation to cell death. JNK triggers mitochondrial permeability transition and releasing of apoptotic factors such as cytochrome c (*e.g.,* acetaminophen hepatotoxicity). In animal models, it was observed that glutathione depletion and covalent binding of NAPQI were insufficient to cause hepatocyte death with hepatotoxic doses of acetaminophen, but JNK was required to actively induce programmed necrosis (Garcie-Cortes et al. 2014).

In the pathogenesis of liver injury, one of the critical underlying factors is mitochondrial dysfunction, which generates alteration of metabolic pathways and mitochondrial damage

(Jaeschke et al. 2012). Drugs (*e.g.,*stavudine and amiodarone) could produce steatosis/steatohepatitis by seriously chancing mitochondrial function (Boelsterli and Lim, 2007). Mitochondrial injury could initiate necrosis and/or apoptosis in liver, leading to activation of cell death signalling pathways, which is exceeded in the mitochondrial death threshold (Han et al. 2013). Age-related regression of mitochondrial function might also hazard energy provide for cellular metabolism and tissue renewal (Chen et al. 2015).

In particular, drugs could damage mitochondrial respiration and/or β-oxidation leading to mitochondrial membrane degradation, which affects mtDNA (Chen et al. 2015). On the other hand, mitochondrial aging, partially due to accumulated oxidative DNA damage, might be affected by host factors including over-nutrition (*e.g.,* obesity, insulin resistance) and alcohol consumption (Stewart et al. 2010).

Social Factors: Alcohol and high fat diets could induce CYP2E1 and CYP4A. Alcohol induces CYP2E1 associated with an enhanced risk of acetaminophen-induced liver injury (Chen et al. 2015). Factors, lowering glutathione stores such as fasting, malnutrition and AIDS, could have an influence on the susceptibility to drug reactions (Korth 2014).

Drugs causing liver injury

Recently, some studies indicate that macrophages could have an important role in solving the liver injury. Chemokines act locally joint with cytokines and cells as idiosyncratic liver injury (Njoku 2014). Alternatively activated macrophages reduce inflammation, and stimulate hepatic regeneration and repair. And, activated macrophages simulated by interleukins (IL-10, IL-4) or tumour growth factors (TGF-β). Additionally, prior studies demonstrated that stem cell-derived tyrosine kinase receptor signalling on macrophages might down regulate inflammation through alternative activation of macrophages (Njoku 2014). In the mechanisms, IL-4 can organize immune responses to diclofenac metabolites that results in diclofenac hepatotoxicity, while IL-6 and IL-10 appease anti-inflammatory responses that may inhibit hepatotoxicity induced diclofenac (Njoku 2014).

The bile salt export pump (BSEP) is a selective bile salts transporter. Certain drugs can block BSEP activity even though BSEP is not directly involved in drug transport. Enhanced hepatocyte exposure to toxic bile salts due to drug-mediated BSEP inhibition raises the risk of idiosyncratic liver injury (Garcia-Cortes et al. 2011).

Drugs affecting transport proteins located at the canalicular membrane could cease bile flow. Specific drugs bind to or disable the bile salt export protein, which causes cholestasis. However, this is little cell injury (Lee 2003). An inhibition of BSEP function causes the accumulation of cytotoxic bile acids in hepatocytes, which induce oxidative stress and/or apoptosis and necrosis by FAS-mediated pathways. Aleo et al. (2014) showed that drugs carrying an important liver injury risk affect both BSEP and mitochondrial activities. Mitochondrial dysfunction could result in decayed ATP production, and in encountering

with BSEP inhibition, and the issue might explain the synergistic connection between mitochondria and ATP-dependent transporters such as BSEP in liver injury (Wu et al. 2011). Multidrug resistance protein (MRP) family, one of hepatobiliary transporters, are also involved in the releasing of conjugated organic anions, bilirubin and drug metabolites (Köck et al. 2014). MRP2/3/4 inhibition could increase the risk in liver injury as compared with BSEP inhibition alone (Köck et al. 2014). As it is well known, bile acids salts are anionic detergents and highly toxic to the cells. In bile, mixed micelle formation with cholesterol, phospholipids, bile pigments, proteins, and inorganic electrolytes protects cholangiocytes from the toxic detergent effect of bile acid salts. Dysfunction of MDR3/ABCB4 has been associated with cholestasis, presumably via inhibition of micelle formation, releasing free bile acids salts in bile (Vree et al. 1998; Chen et al. 2015).

Amoxicillin-clavulanate is the most commonly mentioned medications in liver injury. Also, azathioprine and infliximab are shown to be associated with the highest risk of liver injury (Björnsson and Hoofnagle 2016). In the most studies in DILIN project, antimicrobials, containing antibacterial agents and antituberculosis agents, were approximately 46% of all cases with liver injury (Fontana et al. 2009).

HERBALS AND DIETARY SUPPLEMENTS CAUSING LIVER INJURY

Herbal supplements used for curing disease exist as both raw and commercial preparations. Raw herbal supplements are more frequently used in less developed countries. They are sometimes formulated as a mixture (*i.e.* Chinese herbal medicine), where frequently all ingredients are not known and may include unhealthy contaminants, such as heavy metals, and pesticides. Herbal supplements such as tablets or capsules are mostly used in developed countries. They frequently change in ingredients and concentration of chemical constituents from batch to-batch and also come from different producers (Bunchorntavakul and Reddy 2013).

Some factors increasing use of herbal products such as safety, validity, availability (Abdualmjid and Sergi 2013). Patients with herb-induced liver injury usually have a good prognosis, but acute liver failure with a lethal outcome or the requirement for a liver transplant rarely may occur (Teschke et al. 2013). Some pyrrolizidine alkaloids containing plants such as *Crotalaria*, *Ilexparaguarensis*, *Symphytum*, *Senecio*, *Heliotropium* and *Compositae species* can cause herb-induced liver injury (Teschke and Eickhoff 2015). The pathogenesis of pyrrolizidine alkaloid induced hepatotoxicity has been elucidated in experimental studies, which showed the involvement of CYPs in the activation of pyrrolizidine alkaloids (Larrey and Faure 2011). In a report related with alkaloid poisoning in Afghanistan, more than 2000 people, in which alkaloids were ingested as medicinal herbs or as weed contaminants within cereal grains, have seen liver injury (Korth 2014). Kava is a perennial plant, indigenous to the South Pacific Islands, most frequently used in Western countries as an herbal medicine for the remedy of anxiety and insomnia. In 2005, 55 case reports of kava associated liver injury had been collected by World Health Organization (WHO) (Korth

2014). *Teucrium chamaedrys L.,* known as wall germander, is a small herbaceous, perennial and aromatic plant (Abdualmjid and Sergi 2013). Germander have been used for thousands of years for various disorders, such as dyspepsia, hypertension, gout, diabetes and obesity (Bunchorntavakul and Reddy 2013). Germander includes various ingredients such as saponins and flavonoids. Furan including diterpenoids is well-known to be cytotoxic and carcinogenic. In the studies, the constituents are reported as oxidant via CYP3A4 to reactive metabolites binding to proteins, which deplete cellular glutathione and protein thiols, and ultimately stimulate membrane disruption and hepatocyte apoptosis (Bunchorntavakul and Reddy 2013; Korth 2014; Larrey et al. 1992; Larrey and Faure 2011).

Herbals and dietary products may cause liver injury and are consumed by nearly half of the population in United State and represent excessive amount of trade in worldwide (Navarro and Lucena 2014). Herbalife products (Los Angeles, CA, USA) are distributed via online marketing and through independent sale agents. They are in the form of drinks, tablets, capsules and energy bars for weight control, cosmetics, nutritional support and improvement in well-being. Since 2007, more than 34 cases were reported of herbal life hepatotoxicity from different countries. Hydroxycut is a popular dietary supplement claimed to increase weight loss. Hydroxycut Hard Core include also White Willow extract and Yohimbine (Dara et al. 2008). Several cases were reported of hydroxycut products liver injury. In May 2009, Food and Drug Administration (FDA) issued a warning to stop using hydroxycut products and recalled its products by the manufacturer (Bunchorntavakul and Reddy 2013). Lipokinetix is as dietary supplement for weight loss. Also, lipokinetix marketed by Syntrax Innovations. The supplement includes norephedrine, caffeine, yohimbine, diiodothyronine, and sodium usniate. FDA is warning consumers to immediately stop use of the product lipokinetix. FDA has received multiple reports of persons who developed hepatotoxicity while using lipokinetix (Federal Register 2012). Usnic acid used as a component in weight-loss products. Usnic acid is known to uncouple membrane potential, and stimulates oxidative stress and cell injury. Hepatotoxic cases, resulting in liver transplantation, led to elimination of some usnic acid containing products from the market (Navarro and Lucena 2014). Products provided as mixtures may be particularly dangerous because all components may not be known (Korth 2014).

Nutritional insufficiencies cause epigenetic alterations, which possibly change individual susceptibility in liver injury. Insufficiencies of folic acids, vitamin B_{12}, and choline stimulate methyl donor depletion, which contributes to hypomethylation in the genes in cellular metabolism and hepatocyte differentiation (Chen et al. 2015). Hepatotoxicity resulting from androgenic anabolic steroids causes the typical cholestatic hepatitis. Many reports of products used for body-building and muscle enhancement as a suspected cause for hepatotoxicity have been published (Navarro and Lucena 2014). Vitamin A, cause dose-dependent hepatotoxicity, the spectrum of hepatotoxicity can range from mild liver test elevations with steatosis, to necrosis. Injury usually occurs after exceeding 50,000 IU/day (Navarro and Lucena 2014).

Previous studies show that drugs cause injuries in liver seriously. For that reason some approved drugs were withdrawn. On the other hand some herbal products, which ingredients may not be known, can be particularly dangerous. High and good quality of scientific studies is needed to understand herbal drug-induced hepatotoxicity. The adverse effects of herbs, herbal drugs and herbal supplements should be fully reported to reduce the adverse effects of herbs and herbal products. In this review we compiled that etiologies and risk factors of liver injury, drugs and herbals cause DILI.

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