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A Review of Drug-Induced Hepatotoxicity and Diclofenac Induced Biochemical Changes in Hepatotoxicity

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Abstract - This study was conducted to demonstrate drug-induced hepatotoxicity and Diclofenac-induced hepatotoxicity.The chemical substances which cause liver injury are called hepatotoxins or hepatotoxicants. Hepatotoxicants are exogenous compounds of clinical relevance and may include overdoses of certain medicinal drugs, industrial chemicals, natural chemicals (microcystins), herbal remedies and dietary supplements. The drug-induced hepatotoxicity, at all phases of drug development that includes the pre-clinical toxicity studies, the different phases of clinical trial including the post-marketing surveillance.The Drug Induced Liver Injury (DILI) is defined as the injury caused by exposure to a drug or non-infectious toxic agent and is associated with different levels of organ dysfunction.

Keywords - Drug Induced Liver Injury, hepatotoxicity, Diclofenac, Biochemical

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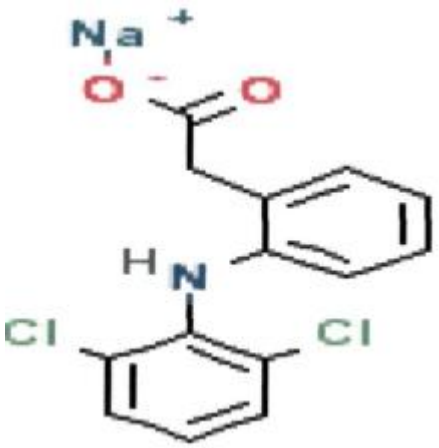
INTRODUCTION

When medications, chemicals, or xenobiotics are introduced to the liver, that is a key organ in drug metabolism, the liver's serum enzyme levels tend to rise. Hepatotoxins are chemicals that cause liver damage. Indiscriminate or nondiscriminatory hepatotoxicity are two possible outcomes. NSAIDs including Ibuprofen, Diclofenac, Sulindac, Aspirin, and Paracetamol, which are commonly used for anti-inflammatory and analgesic purposes, as well as hepatotoxic anti-tubercular medicines (Isoniazid, Rifampicin, Pyrazinamide), have been linked to liver toxicity, and this is a major cause for concern. NSAIDs raise a lot of red flags because they fall into the non-prescription, over-the-counter (OTC) drug category. Since most of these medications are uTILIZED for long-term treatment, toxicity has been a major worry, which has led to the withdrawal of the preparations from the market or the discontinuation of clinical trials. N-Acetylcysteine, in specific Acetaminophen toxicity, has been shown to prevent hepatocyte necrosis & fibrosis in the liver, that is a common occurrence in cases of liver injury. Like Methionine, another important amino acid, it has been discovered to be an effective hepatoprotective agent and is being considered as a therapy option for many diseases. Therefore, this study was conducted to demonstrate its hepatoprotective impact on Diclofenac-induced hepatotoxicity.

NSAIDs, or nonsteroidal anti-inflammatory medicines, are medications with analgesic, antipyretic, & anti-inflammatory properties when used in larger doses. NSAIDs are non-narcotic analgesics. These medications are distinguished from steroids by the term "nonsteroidal," which refers to their lack of the anti-inflammatory and depressant properties of eicosanoids. Signaling molecules derived from the oxidation of essential fatty acids are referred to as eicosanoids (EFAs). Inflammatory processes and the body's defence mechanisms are under their control, and they also serve as messengers in the central nervous system. Prostaglandins, prostacyclins, thromboxanes, &leukotrienes are all members of the eicosanoid family. Cu-3 & aj-6 EFAs are used to make these. Propionic acid derivatives, acetic acid derivatives, enolic acid (Oxicam) derivatives, fenamic acid derivatives, & selective COX-2 inhibitors are some of the most common NSAIDs (Coxibs). Anti-inflammatory medicine (NSAID) Diclofenac is used to relieve inflammation and as an analgesic for disorders such as arthritis & acute injury. Dysmenorrhea can be alleviated by using it. 2-(2-(2,6-dichlorophenyl) amino)phenyl) acetic acid, the molecular weight of which is 296.148 g/mol, is the IUPAC designation for the acetic acid derivative that gives diclofenac its popular name. Its half-elimination time is between 1.2 and 2 hours. In 1979, Diclofenac was introduced in the United Kingdom for the first time (Salmann, 1986). In China, sodium salt is the most common kind, but it can also be found in the United Kingdom, India, and the United States.

NSAIDs, despite the fact that they reduce bone growth, healing, and remodelling, are still given as

analgesics for patients with healed fractures (Nair et al., 2006). Diclofenac is a widely utilized medicine for the treatment of inflammatory disorders such as rheumatoid arthritis, osteoarthritis, or acute muscular pains, despite the fact that its mechanism of action is unknown. Analgesic, antipyretic, & anti-inflammatory actions of diclofenac can be attributed to its ability to inhibit both COX-1 & COX-2 isoenzymes by preventing arachidonate binding (Mc Cormack and Brune, 1991).



Chemical structure of diclofenac sodium

BACKGROUND OF THE STUDY

The safety and efficacy of the drugs used in the treatment of various clinical conditions in any individual remains complex and multifactorial and difficult to Analyse or identify the suspected drug that causes the Adverse Drug Reaction (ADR).

- **Role of liver in drug-induced hepatotoxicity:**

Liver being a principle organ for playing several vital roles in the body, is involved in several biochemical pathways, metabolism of nutritional factors, metabolizing the administered drugs or any substance that is ingested, which could be either herbal or even natural chemicals. Thus, making it important to observe, for the drug-induced hepatotoxicity, at all phases of drug development that includes the pre-clinical toxicity studies, the different phases of clinical trial including the post-marketing surveillance.

There are several levels of organ dysfunction linked with the DILI, which is induced by exposure to a pharmacological or non-infectious hazardous substance. As a result of advances in study at the molecular level, it is still difficult to identify & diagnose the suspected chemical that causes Drug induced Liver Injury.

- **Types of drug induced liver injury:**

The drug induced liver injury are mainly of two types: (1) Dose-dependent, which is also called as predictable, direct toxicity, reproducible and occurs after the consumption of the drug that exceeds a known toxic threshold level. In such cases, the liver injury that occurs is proportional to the administered dose, example Paracetamol; (2) while the Dose-independent Drug induced Liver Injury is also called as unpredictable and idiosyncratic that occurs even at the therapeutic doses, and the liver injury caused is not always proportionate to the administered dose, further, the time of damage, onset could also vary example Diclofenac, Sulindac, Trovafloxacin.

- **Risk factors of DILI:**

With a wide range of drugs, including Antimicrobials, NSAIDs, Antiepileptic, Antipsychiatric drugs etc., causing the drug induced liver injury, several factors are known to influence the drug induced liver injury, and are hence considered as the risk factors these includes; the age, gender, alcohol, concomitant use of drugs, nutrition, HIV, genetic factors, the dose and the body mass of the individual.

- **Evaluation of drug induced liver injury:**

Apart from the clinical evaluation, the diagnosis includes the causality assessment to identify the suspected drug; evaluation of the biochemical parameters which indicate the liver functioning status, and further; the histopathological studies to reveal and confirm the clinical diagnosis. Liver imaging can also remain the infiltrative hepatic diseases & fatty live diseases. The histopathological information could be drug-specific and would indicate the severity and latency of the biochemical pattern.

Although, 90% of recoveries have been registered on discontinuation of the drug, some may progress with the outcome as chronic liver disease. The prognosis has been poor in women, elderly, individuals with pre-existing liver disease; those habituated to alcohol and individuals with genetic defect. Hence, it is always important to monitor the liver enzymes which are indicative of the hepatotoxicity.

- **Treatment of drug induced liver injury:**

Discontinuation of the medicine in question, followed by treatment with certain drugs, is the primary treatment for DILI. There are very few medications available for treating DILI. This antidote, known as N-Acetylcysteine (NAC), is used to refill the body's Glutathione levels after exposure to either Paracetamol or Acetaminophen toxicity. Therapeutic of DILI has also included theutilize of Corticosteroids & Antihistamines, Cholestyramine& L-Carnitine, Folic Acid, Methionine, &Ursodeoxycholic Acid as symptomatic treatment options.

DRUG INDUCED LIVER INJURY

DILI is an extremely rare but potentially deadly adverse reaction to drugs. (Lee WM ET AL 2013). The crude yearly occurrence of DILI post-marketing ranged from 2.4 to 13.9 per 100000 inhabitants in population-based studies employing different techniques & cut-offs (Sgro et al. 2002). Acute liver failure due to DILI is the most common cause of post-marketing limitations or product withdrawals in North America & Europe, as well as the major motive medications fail to receive marketing authorization. J.L. Stevens & colleagues Life-saving treatments like cancer therapies are taken cautiously because there are no other options or because their benefits outweigh their hazards. Almost any known kind of liver illness can be misdiagnosed as DILI. There are a number of well-known phenotypes, characterised by clinical and pathological criteria, that are recognised. For example, (Fontana RJ 2010) Acute hepatocellular damage has been the most commonly observed & investigated, but other types of DILI are now understood to be just as dangerous, if not more so. When a patient has advanced liver disease, DILI is likely to have a worse outcome. (N. Chalassani et al. 2016) There are three types of DILI events: intrinsic (related to toxic exposure levels of the drug or its metabolites) and idiosyncratic (rare & unexpected given the drug's pharmacological action & linked to a yet poorly understood interplay of individual host susceptibility-related & other factors). "Indirect" DILI events are those that aren't directly linked to the drug itself (linked to an unwanted biological action of a drug in an individual patient). (Hoofnagle JH 2019) No biomarkers exist for DILI risk in people at this time. Although genetic studies have discovered some HLA alleles that are related with DILI owing to several medicines, they have little predictive value.

N-ACETYL CYSTEINE OUTLINE

L-cysteine is the source of N-acetyl cysteine. Proteins are constructed from amino acids. Medicinal applications for N-acetyl cysteine are numerous. Acetaminophen (Tylenol) & carbon monoxide poisoning can both be treated with N-acetyl cysteine, which is taken orally as an antidote. Additionally, it is used in the treatment of chest pain (unstable angina) and bipolar disorder, An eye infection called as Keratoconjunctivitis and flu-like symptoms are among the other conditions that can cause bile duct obstruction in newborns and also Alzheimer's disease and allergic reactions to the anti-psychotic phenytoin. People with severe kidney illness have lower levels of lipoprotein (a) &homocysteine (perhaps a risk factor for heart disease), as well as lower rates of heart attack and stroke.

It is also taken by mouth for hepatitis, kidney disease, hearing loss & ulcerative colitis. Polycystic ovary syndrome (PCOS), low blood pressure, lupus, muscle damage owing to exercise as well as lupus-induced muscle damage, schizophrenia & recovery after surgery are some of the other conditions for which N-acetyl cysteine is used. ALD, EPP, and Hereditary Hemorrhagic Telangiectasia (HHT) are all treatable with this medicine.

LIVER

Liver is an essential organ of the body and is involved in the vital functions, to maintain the internal homeostasis. The main function of which is synthesis and secretion of bile into the gallbladder and second part of the duodenum, where it is playing an important role of metabolizing all the ingested substances, which may be in the form of food, nutrients, drugs or chemicals. Liver synthesizes many essential proteins, stores the nutrients that are released into circulation at the time of starvation and detoxify the ingested harmful substances in the process of metabolism, hence, considered as a vital organ of the body.

Liver is involved in the metabolism of the major nutrients such as carbohydrate, fats, proteins and both the fat soluble and water soluble vitamins. It plays a pivot role in the metabolism of urea, iron, and alcohol. Further, it is involved in the synthesis of several proteins including the clotting factors, those mediated in the process of inflammation, the hormone binding proteins, lipids, carbohydrates, vitamins and bile salts. It is considered as a storage site for glucose, proteins, fats and vitamins which are released for utilization during the scarcity, while they are stored when they are in excess. It is considered as a major organ involved in detoxifying the chemicals and the toxins released from the infecting organisms which are neutralized in the liver. It is known to degrade/metabolize the drugs, enzymes, hormones, cytokines and various other chemicals.

HEPATOTOXICITY

Drugs are responsible for 2- 5% of cases of jaundice patients and around 10% of acute hepatitis cases (Deterding et al., 2017). Cirrhosis and chronic liver disease responsible for 2% of mean among 17 countries with approximately 40,000 deaths in one year (Sarpal et al., 2016). Considering the significance of DILI as a foremost reason of liver damage, studies throw light on numerous drugs that induce hepatotoxicity, through their mechanism of hepatic damage and clinical development (Dara et al., 2016). One among the most common reason of poisoning can be caused by paracetamol toxicity. When given in therapeutic doses, paracetamol is defined as comparatively nontoxic while it is identified to result in toxicity when consumed in a single or frequent high dose, or after chronic ingestion. Hepatotoxicity can also be caused by frequent supratherapeutic misuse, deliberate ingestion and non-intentional misuse which lead to cause acute liver failure (ALF) in the Europe and US. Almost half of ALF cases can be caused by paracetamol in US that remains as one of the leading causes of liver transplantation. The study resolute paracetamol toxicity with specific attention

to the facets of hepatic damage and related fatalities (Tittarell et al., 2017).

FACTORS INDUCING HEPATOTOXICITY

The liver has a major role in converting and clearing chemicals and is accountable to the toxicity from many intrinsic and extrinsic factors. Few medicinal agents, when consumed in overdoses and at times even when presented within therapeutic ranges, might results in organ damage. Other chemical agents used in industries and laboratories also induce hepatotoxicity. Such a vital organ, essential for human existence must be well protected and must be well maintained which is sometimes prone to damages and diseases (Seif, 2016). Whilst mankind is exposed to a vast array of foreign compounds through environmental exposure, consumption of contaminated food or exposure to chemicals in the occupational environment and is sometimes abused by these alcohol consumption, environmental toxins, poor eating habits, recommended and other drug usage, which can damage and weaken the liver and eventually lead to hepatitis and cirrhosis. Liver structure and functions are being affected by alcoholic liver diseases where its physiological role like the biotransformation of lipophilic compounds to water soluble derivatives are also main concern (Massart et al., 2017).

DRUG-INDUCED HEPATOTOXICITY

An overdose of pharmacological agents or xenobiotics can lead to hepatotoxicity, which is a type of liver malfunction, liver damage, or chemically-induced liver damage. Hepatotoxins or hepatotoxicants are the chemical chemicals that induce liver damage. There are a variety of exogenous hepatotoxicants that can have clinical significance, including overdoses of medications, industrial chemicals, natural chemicals (such as microcystins), herbal medicines, or nutritional supplements.

Even when medications are utilized within therapeutic ranges, hepatotoxicity due to drug administration can occur, and minorities of pharmaceuticals have predictable dose-dependent liver injury. This may be due to the main substance itself, a reactive metabolite, or an immune-mediated response that ultimately affects the hepatocytes, the biliary epithelial cells, and/or the liver vasculature. An enzyme's expression or blood cofactor concentration gradient might affect its ability to cause hepatotoxicity, which is dependent on the concentration of hepatotoxicants present.

HERBAL AND DIETARY SUPPLEMENT (HDS) INDUCED LIVER TOXICITY

Apart from the medicines, the current trend of using therapeutic agents is observed to be with the herbal preparations, which amounts to 80% of the world's population who prefer the herbal preparations for therapeutic purposes, as shown by the World Health Organization (WHO) estimate in 1998 **[31].** This has been a traditional practice in some parts of the world, mainly in the east or Africa. The herbal preparations may have no pharmacological properties even if recognized as medicines, therefore, although they could be beneficial, they would also have toxic and adverse effects. Similar to other medicines, the herbal preparations are likely to cause the liver toxicity which can be either direct or idiosyncratic.

CLASSIFICATION OF DRUG INDUCED LIVER INJURY

- **According to causative agents:**

The drug induced liver injury can be classified according to the causative agents, as medications, herbs, health foods or dietary supplements, folk remedies, combined and others. Further, the herbs can be sub-categorized as herbal preparations, herbal medications, or medicinal herbs or plants.

- **According to prescription:**

They can also be classified as either prescription medications or non-prescription medications caused drug induced liver injury.

- **Folk remedies:**

They can also be categorized as those caused by the folk remedies, the traditional remedies which do not fit into herbal medications and herbal preparations but cause the liver injury are categorized as folk remedies; while the preparations which are intended to supplement the diet and provide the nutrients in the form of vitamins, minerals, fibers, fatty acids, amino acids, etc., which may be either deficient or may not be consumed in sufficient quantities, such supplement-induced liver injury, can be categorized as health foods or dietary supplements injury.

- **Based on Adverse Drug Reaction:**

However, as an adverse drug reaction, the drug induced liver injury may be further divided into idiosyncratic reactions and non-idiosyncraticreactions (predictable) and they tend to be dose-related for e.g. hepatotoxicity due to Paracetamol overdose. However, the unpredictable reactions, occurring in less than 1% of the exposed, are generally considered to be independent of the dose administered.

DICLOFENAC INDUCED BIOCHEMICAL CHANGES IN HEPATOTOXICITY

The acute toxicity of diclofenac sodium was analyzed by observing the death rate, clinical signs and symptoms, and variations in blood biochemistry. Biochemical findings showed increase in creatinine, uric acid and plasma glutamic pyruvic transaminase, and reduction in total protein and albumin at 12h and

24 h post-treatment which returned to the normal levels at 36 h post-treatment. The biochemical variations at 12h and 24 h posttreatment showed wide visceral gout with distinguishing histopathological lesions in kidney, spleen, heart, liver, and intestine on necropsy findings. The results specified that diclofenac sodium has nephrotoxic, hepatotoxic, and visceral gout triggering effects in the experimental animal, specifically at 20 mg/kg (Teenu et al., 2009). Either through cholestatic hepatitis or through acute drug-induced hepatitis, DILI can progress (de Boer et al., 2017). Degenerative variations in the liver cells, including their cholestasis, steatosis and necrosis can be instigated by the toxic effect of drugs (Kwong et al., 2019). There are 3 main mechanisms of DILI (1) direct cell damage, (2) hindrance of mitochondrial beta-oxidation and the mitochondrial respiratory chain, and (3) immunologic reactions (Noureddin, Kaplowitz 2016). The signs of toxic effect of drugs found in the histopathological analysis including the toxic effect, inflammatory infiltrates in the portal tracts, Kupffer cells, or stellate cell activation (Brunt, 2016). The mechanisms elucidating drug-induced hepatic damage include oxidative stress and mitochondrial damage (Chen et al., 2015; Porceddu et al., 2018).

DICLOFENAC INDUCED OXIDATIVE STRESS

Parallel antioxidant defences have been developed by most species to counteract the effects of nitrogen and oxygen radicals. When the balance between ROS and RNS is disrupted, these defences are compromised, resulting in oxidative stress (Fattori et al., 2017). Proteins, nucleic acids and lipids can be covalently altered by ROS/RNS in cells. A small number of studies have recently revealed the importance of ROS/RNS in cell signalling. Specifically, DILI are of interest in these matters. Hepatotoxicity and oxidative stress have been implicated in numerous hepatotoxic medication mechanisms that have been removed off the market (Foufelle and Fromenty, 2016; Banarjee et al., 2017). When acetaminophen is used, the uneven production of ROS and RNS arises from the covalent protein modification, which can damage mitochondria & disrupt apoptotic pathways. This leads to increased oxidative stress & damage, which perpetuates itself. In addition, idiosyncratic liver damage may be caused by subclinical oxidative stress in mitochondria (Dara, 2016). A better knowledge of oxidative stress in vivo would help enhance preclinical & primary clinical testing of innovative medications to better predict liver injury & oxidative stress and to better choose antioxidants for human use with a variety of disorders (Lancaster et al., 2015; Du et al., 2016). Liver tests may be affected by drug-induced hepatotoxicity. NSAIDs associated with hepatotoxicity have a relatively low incidence rate. To provide an accurate picture of hepatotoxicity's true occurrence rate, the premarketing studies planned to evaluate NSAIDs' efficacy and safety may not have a large enough sample size. NSAIDs are a major cause of DILI because of their widespread use. It is recommended that NSAIDs, particularly diclofenac, be used at the lowest effective dose possible to minimise the risk of hepatotoxicity and that safer NSAIDs be used instead.

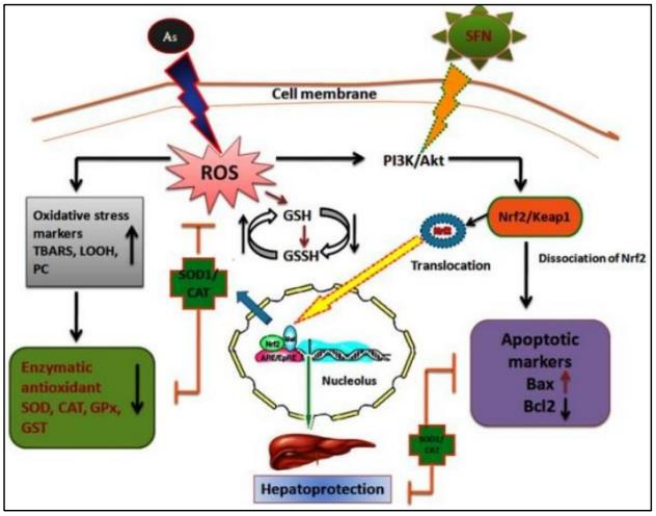


Figure 1: Diclofenac induced oxidative stress

CONCLUSION

DILI is an extremely rare but potentially deadly adverse reaction to drugs. Drug-induced liver injury (DILI) is a type of DILI that happens in an extremely tiny percentage of people who take the drug and is unanticipated from its recognised pharmacological effects.Hepatotoxicity refers to the liver dysfunction, liver damage or to the chemical-driven liver damage associated with an overload of medicinal agents or xenobiotic.The hepatotoxicity caused by the administered drugs may sometimes occur even when they are used within therapeutic ranges, while minorities of the drugs have predictable dose-dependent liver injury.It is difficult to diagnose the drug induced liver injury due to the lack of specific signs & symptoms and tests. The manifestations vary to range from an asymptomatic elevation of liver enzymes to fulminant hepatic failure. Hence, the causality assessment of drug induced liver injury becomes difficult.

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