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Review Article

An Insight about Diclofenac Induced Hepato-renal Toxicity

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ABSTRACT

Background: Diclofenac is a medication that has received FDA approval for treating and managing acute and chronic pain brought on by inflammatory disorders, particularly those that affect the musculoskeletal system. Although diclofenac (DIC) has many beneficial therapeutic uses, it also carries the potential of serious adverse effects, such as kidney damage, liver damage, gastrointestinal problems and cardiovascular hazards. We aimed to present an Insight about Diclofenac-induced hepato-renal toxicity. **Conclusions:** Diclofenac is the NSAID most frequently implicated in hepatocellular and renal injury development. Diclofenac sodium damages hepatic and renal tissues by generating malondialdehyde (MDA) and reducing glutathione (GSH) in hepatic tissues. This oxidative stress leads to the secretion of cytochrome c, which activates the caspase cascade and causes hepatocytes to undergo apoptosis. Diclofenac's main harmful mechanism involves mitochondrial oxidative stress and ROS generation. Lysosomal dysfunction and impaired autophagy flux are brought on by intracellular ROS, which prevents the efficient destruction of damaged mitochondria to stop the creation of more ROS. Hepatotoxicity and cellular oxidative stress are made worse by the vicious loop of mitochondrial damage and impaired autophagy.
Keywords: Diclofenac, Hepatotoxicity, Renal Toxicity.

INTRODUCTION

Hepatotoxicity

When all other causes of liver injury have been ruled out, drug-induced liver injury (DILI) is defined as liver damage brought on by a range of widely used drugs, herbal remedies or nutritional supplements [1]. Although DILI is uncommon in the general population, it is steadily rising in frequency among hospitalized patients, particularly in those with unexplained liver diseases [2]. Drug-induced liver damage is the most common cause of acute liver failure in most western countries, accounting for more than half of cases and accounting for 3–5% of hospital admissions for jaundice [3]. Furthermore, statistics show that from 1953 to 2013, drug-induced liver injury accounted for 18% of drug withdrawal worldwide [4]. Drug-induced liver injury can be distinctive, intrinsic, or indirect. Intrinsic DILI is characterized by a drug's or its metabolite's direct cytotoxic activity. It develops in a dose-dependent way and its occurrence may be anticipated with reasonable ease. Contrarily, idiosyncratic DILI is dosage-independent and cannot be anticipated to occur [5].

When a medicine affects the immune system or liver indirectly, it might result in indirect liver damage [6]. Moreover, hepatocellular, mixed or cholestatic hepatitis is the pathological classification of DILI based on the target cells of the liver affected by the drug (i.e., hepatocytes, bile duct epithelial cells, hepatic vascular or sinusoidal endothelial cells) [7].

"Intrinsic" and "idiosyncratic" DILI are both exacerbated by a wide variety of risk factors; these include, but are not limited to, inflammation, gender, age, comorbidity, gut microbiota, lifestyle factors and antioxidation defense, immune response, liver regeneration, and transporters. Since drug lipophilicity might increase hepatocyte drug absorption and reactive metabolite buildup, it is also linked to DILI risk [8].

The liver's crucial function in the biotransformation (metabolism) of xenobiotics entering the gastrointestinal tract is likely the primary factor

explaining its susceptibility to negative drug responses [9]. Risk factors alter the hepatic metabolism and excretion of the substance that causes DILI, which causes cellular stress, cell death, activation of an adaptive immune response and a failure to adapt, which progresses to overt liver injury [9]. Also, drugs or reactive metabolites can cause intrinsic predictable toxicity by covalently binding to intracellular proteins, generating reactive oxygen species (ROS) and inducing organelle stress (such as endoplasmic reticulum (ER) and mitochondrial stress). If the stress is minor, organelle adaptive responses (such as unfolded protein responses in the ER or mitochondria) will compensate and the development of the injury will be dampened. If these responses are overwhelmed, organelle stress can activate the intrinsic pathway of apoptosis via mitochondrial outer membrane permeabilization (MOMP) or lead to necrosis by mitochondrial permeability transition (MPT) and cell death will occur [10]. Additionally, the innate immune response from drugs can worsen tissue damage. Damage-associated molecular patterns (DAMPs) generated by drug-damaged hepatocytes can activate innate immunity, causing inflammation in the absence of infectious pathogens, or "sterile inflammation." Kupffer cells (KCs), a kind of liver-resident macrophage, are among the immune cells in the liver that DAMPs activate. ProIL-1 and proIL-18 are produced from activating KCs; these molecules are then cleaved by caspase-1 intracellularly and released as mature IL-1 and IL-18, respectively. Together with pro-inflammatory chemokines, IL-1 modulates neutrophil and monocyte recruitment and intensifies the inflammatory response by activating infiltrating leukocytes [11]. Inflammasomes play a critical role in the immune response, which is stimulated by damage-associated molecular patterns (DAMPs) and neoantigen presentation on particular human leukocyte antigen (HLA) molecules initiates the adaptive immune response [6].

Nephrotoxicity

Medication-induced kidney damage, whether direct or indirect, is referred to as drug-induced nephrotoxicity. Some of the manifestations associated with glomerular and tubular injury, respectively, include nephrotic syndrome, hydroelectrolytic disorders (HED) and acute or chronic lower glomerular filtration rate (GFR) [12].

A common clinical problem is drug-induced nephrotoxicity, often referred to less frequently as drug-induced kidney disease (DIKD). Estimates indicate that 14–26% of patients in the adult population and 16% of pediatric patients may be affected [13] and by 2040, kidney diseases are anticipated to rank as the sixth largest cause of mortality [14].The third most common cause of acute kidney disease (AKD), which has gotten worse recently due to the growing use of drugs that can harm the kidneys, is nephrotoxicity. According to studies, up to 20% of the time, critically ill patients take nephrotoxic drugs [12].

Several factors, such as the inherent nephrotoxicity of pharmaceuticals, underlying patient characteristics that enhance their risk for kidney injury and the metabolism and pathway of kidney excretion of the various substances given, all increase the risk of drug-induced nephrotoxicity [15]. By raising the drug concentration to a dangerous level, volume depletion increases the risk. Hypoalbuminemia, a condition typically observed in cirrhotic patients, increases the serum levels of the unbound drug fractions, increasing the risk of an unintended medication overdose.

Older people and neonates are particularly vulnerable to drug-induced nephrotoxicity. The genetic makeup of an individual, which defines their unique metabolic pathways and drug sensitivity, may also impact how their kidneys are vulnerable to nephrotoxicity [16].

Diclofenac induced Hepato-renal toxicity.

Diclofenac (DIC) is one of the most commonly used nonsteroidal anti-inflammatory drugs (NSAIDs). Despite its extensive therapeutic utility, diclofenac may cause multiple severe side effects, including renal injury, hepatotoxicity, gastrointestinal injury and cardiovascular risks [17]. DIC induces the broad suppression of prostaglandins by inhibiting cyclo-oxygenase 1, which has a protective function in the kidneys and other organs (PG). According to reports, DIC inhibits PG production, which lowers glomerular filtration rate (GFR) and other renal functions in a dose-dependent way [18].

Diclofenac works by preventing the production of prostanoids such as prostaglandin-E2 (PGE2), prostacyclins, and thromboxanes, which are crucial elements of the inflammatory and nociceptive response via inhibition of the activity of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). Arachidonic acid's ability to bind to COX-1 and COX-2 is competitively suppressed. Although data suggests that diclofenac selectively inhibits COX-2, around four times more than COX-1, during in vitro testing, diclofenac inhibits COX-1 and COX-2 pretty similarly [19].

Diclofenac can inhibit the thromboxane-prostanoid receptor, affect arachidonic acid release and uptake, inhibit lipoxygenase enzymes and activate the nitric oxide-cGMP antinociceptive pathway. Other novel mechanisms of action may include the inhibition of substrate P, inhibition of peroxisome proliferator-activated receptor gamma (PPARγ), blockage of acid-sensing ion channels, alteration of interleukin-6 production and inhibition of N-methyl-D-aspartate (NMDA) receptor hyperalgesia [20].

It is well recognized that overdosage of diclofenac reduces glutathione conjugation, which harms the mitochondrial transmembrane. These produce toxic byproducts and decrease antioxidant activity, which results in peroxidative damage to cellular membranes, necrosis and decreased ATP generation [21].

Through the generation of malondialdehyde (MDA) and the depletion of Glutathione (GSH) in hepatic tissues, diclofenac sodium causes hepatocellular and renal damage. This oxidative stress causes the release of cytochrome c, which then triggers the activation of the caspase cascade and apoptosis of hepatocytes [22].

Diclofenac's main harmful mechanism involves mitochondrial oxidative stress and ROS generation. Lysosomal dysfunction and impaired autophagy flux are brought on by intracellular ROS, which prevents the efficient destruction of damaged mitochondria to stop the creation of more ROS. Hepatotoxicity and cellular oxidative stress are made worse by the vicious loop of mitochondrial damage and impaired autophagy [23]. Additionally, diclofenac causes mitochondrial dysfunction in the liver through multiple pathways, including decreasing ATP levels, opening the mitochondrial permeability transition pore, uncoupling oxidative phosphorylation, and increases in cytosolic calcium and reactive oxygen species (ROS) [24].

By specifically targeting the kidney's mitochondria, diclofenac may cause renal damage by increasing the formation of reactive oxygen species (ROS), apoptosis and DNA damage [25]. Nuclear factor (NF)-B transcription is triggered by the produced reactive oxygen species (ROS), which increases inflammatory responses and causes acute kidney injury to proceed further [26].

DIC treatment may cause renal injury because it reduces renal blood flow, which causes ischemia and necrosis, as well as increased oxidative stress and the release of inflammatory cytokines [۲7].

Cellular infection or stress triggers a multiprotein platform called the NLRP3 inflammasome. Its activation triggers the release of proinflammatory cytokines like interleukin-1 (IL-1) and IL-18, as well as pyroptosis, an inflammatory form of cell death and by aiding in the priming process, ROS encourages NLRP3 inflammasome activation [28].

Drug-damaged hepatocytes & kidney cells can produce damage-associated molecular patterns (DAMPs), which can activate innate immunity and cause "sterile inflammation" in the absence of infectious microorganisms [11].

In response to Pathogen associated molecular patterns (PAMPs) or DAMPs, NLRP3 forms the NLRP3 inflammasome. This macromolecular complex binds to caspase-1 through the apoptosis-associated speck-like protein with a caspase recruitment domain (ASC). This macromolecular complex triggers the release of proinflammatory cytokines and caspase-1-dependent pyroptosis [29].

The 28-day exposure to daily DIC administration led to increased body weight, exaggerated inflammatory responses, altered normal hematological parameters, abnormal liver and kidney functions, triggered oxidative stress release and suppressed antioxidant levels, as well as elevated serum levels of AST, ALT, urea and creatinine linked to elevated lipid peroxidation (LPO), NO and TNF levels of both liver and kidney tissues [30].

Asymmetry between the molecular processes that control oxidative stress, inflammation, autophagy and cell death contributes to acute and chronic kidney disease. The etiology of DIC-induced acute kidney injury was mostly attributed to defective renal autophagy, which likely involves downregulation of the AMPK system. Autophagy is negatively regulated by the mammalian target of rapamycin (mTOR) [31].

New remedies for diclofenac-inducedhepatorenal toxicity

By lowering blood levels of liver enzymes and renal criteria, artemisia may help lessen the harmful effects of diclofenac on the kidney and liver. The remarkable properties of regulating ROS are present in the Artemisia plant. They occasionally significantly impact hydrogen peroxide and hydroxyl ions' abilities to act as antioxidants and radical scavengers. Additionally, they might provide effective defense by improving antioxidant performance and minimizing ROS formation [32]. Additionally, in male rats, silymarin reduces the liver damage caused by diclofenac by reducing inflammation and oxidative stress [33].

In rats, diclofenac sodium-induced hepato-nephrotoxicity may have been prevented by allicin. Allicin is regarded as the most significant biologically active component in freshly crushed garlic extract. According to studies, allicin contains anti-microbial, antioxidant, anti-inflammatory, anti-hypertensive, anti-cancer, anti-genotoxic, and anti-apoptotic properties [22].

Ajwa date extract is a nutritional supplement that is safe, tissue-protective, and reduces the effects of acute diclofenac toxicity on cells and tissues [34]. It was shown that before taking diclofenac, treatment with virgin coconut oil (VCO) for 21 days reduced histological renal damage and restored antioxidant enzyme activity and TNF- levels in the kidney, suggesting that VCO may be useful in preventing diclofenac-induced nephrotoxic damage [35].

Furthermore, in the rat model of diclofenac-induced kidney damage, quercetin improved conditions by reducing the inflammatory response and controlling oxidative stress. Through the application of their anti-oxidative and bioactive phytochemicals, folic acid and lentil extract may be able to significantly reduce the risk of unfavorable hematological, kidney tissue oxidative stress and renal dysfunction brought on by diclofenac In the rat model [36].

Royal jelly significantly improved the hepatic and renal functions in the rat model of diclofenac-induced toxicity. PGE-2 contents and COX-2 expression were also significantly increased and the histopathological images of the hepatic, renal, gastric, and intestinal tissues were also improved [37].

The antioxidant defense system and liver tissue were negatively affected by DIC. Still, GSH, GPx, SOD and CAT levels were significantly increased and protein carbonyl, AST, ALP, ALT, total bilirubin, MDA, serum IL-1, and IL-1 gene expression were significantly decreased after oral administration of gallic acid [38].

In male albino rats, cinnamon aqueous extract reduced the hepato-renal toxicity caused by diclofenac sodium and modified oxidative stress, cell apoptosis and inflammation [39]. Also, betanin may have had anti-inflammatory and antioxidant effects against diclofenac-induced hepato-renal damage [40].

By reducing oxidative stress and inflammation, mandarin peel ethanolic extract reduces diclofenac sodium-induced hepatorenal damage in rats [41]. Daily caffeine administration improved diclofenac toxicity in the kidney and liver by three pathways, including the inhibition of DNA damage, anti-inflammatory and antioxidant effects [30]. In a rat model of diclofenac-induced kidney injury, carvacrol has a nephroprotective effect via controlling oxidative stress and reducing inflammatory response [42].

All biochemical and molecular characteristics brought on by DIC were successfully facilitated by pretreatment with aprepitant. Aprepitant also prevented the DIC-activated Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling in renal tissues while restoring the decline in renal PGE-2 levels [43].

CONCLUSIONS

Diclofenac is the NSAID most frequently implicated in hepatocellular and renal injury. Diclofenac sodium damages hepatic and renal tissues by generating malondialdehyde (MDA) and reducing glutathione (GSH) in hepatic tissues. This oxidative stress leads to the secretion of cytochrome c, which activates the caspase cascade and causes hepatocytes to undergo apoptosis. Diclofenac's main harmful mechanism involves mitochondrial oxidative stress and ROS generation. Lysosomal dysfunction and impaired autophagy flux are brought on by intracellular ROS, which prevents the efficient destruction of damaged mitochondria to stop the creation of more ROS. Cellular oxidative stresses mediated Hepatotoxicity and nephrotoxicity are made worse by the vicious loop of mitochondrial damage and impaired autophagy.

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