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Nephrotoxicity and hepatotoxicity associated with non-steroidal anti-inflammatory drugs

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Abstract
Non-steroidal anti-inflammatory drugs (NSAIDs) including both traditional non-selective NSAIDs and the selective cyclooxygenase (COX)-2 inhibitors, are widely used for their anti-inflammatory and analgesic effects. NSAIDs are a necessary choice in pain management because of the integrated role of the COX path way in the generation of inflammation and in the biochemical recognition of pain. NSAIDs are the competitive inhibitors of cyclooxygenase (COX), the enzyme which mediates the bioconversion of arachidonic acid to inflammatory prostaglandins (PGs). Disruption in PGs production affects the kidneys in several ways, including vasoconstriction that may result in ischemic acute kidney injury (AKI) in at-risk patients. They also impair salt and water excretion, leading to oedema and hypertension. Other complications include hyperkalemia, hyponatremia, nephrotic syndrome, acute interstitial nephritis and chronic kidney disease progression. AKI from NSAIDs is usually reversible with favourable prognosis after discontinuation of NSAIDs. Avoidance of NSAIDs exposure is extremely important, especially among high-risk patients. NSAIDs have been associated with hepatic side effects; however, the frequency of these side effects is uncertain. Physicians and hepatologists must be vigilant to the hepatotoxic potential of any NSAID, as increased awareness, surveillance and reporting of these events will lead to a better understanding of the risk factors and the pathophysiology of NSAID-related hepatotoxicity. This review can be used for further research as well as clinical purpose.

Keywords: Non-steroidal anti-inflammatory drugs, nephrotoxicity, hepatotoxicity, acute kidney injury, prostaglandins.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly prescribed drugs that are accounted for 5-10% of all prescriptions in the United States [1]. Acetyl salicylic acid (ASA) is the first agent that was discovered in 1893 [2]. Since then, many agents have been developed and widely used for various conditions. NSAIDs exert their anti-inflammatory effect via cyclooxygenase (COX) inhibition [3].

The kidneys receive approximately 25% of the cardiac output and are the major organ for drug excretion. Due to this function, the renal arterioles and glomerular capillaries are especially vulnerable to the effects of drugs. Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly used over-the-counter (OTC) medications in the United States and are known to have adverse effects on kidney function [4]. OTC NSAIDs, including ibuprofen, are routinely administered to children or taken by teenagers for pain and fever. Use of NSAIDs has increased dramatically during recent years, especially in children in the United States. Because of their frequent and accepted use, NSAIDs are widely considered safe, but in reality, even therapeutic doses carry a risk of loss of renal function [4, 5].

Non-steroidal anti-inflammatory drugs (NSAIDs), often prescribed in medical practice as analgesic, antipyretic and anti-inflammatory agent, are among the most widely used drug classes worldwide. Recent studies point to NSAIDs as the most effective drugs, for example, for the treatment of pain associated with renal calculi, being better even than opioids. The main consumers of this group of drugs are individuals afflicted by chronic pain, usually associated with rheumatologic diseases, including rheumatoid arthritis, osteoarthritis and other musculoskeletal disorders [5]. The pharmacological action of NSAIDs depends on the dose and duration of use, which predisposes the involvement of specific organs, and the second one most affected are the kidney. Therefore, it is one of the drugs that, if used in the long term, increases morbidity, especially for the elderly, since they use several other medications (antihypertensives, antidepressants, anticoagulants) that may cause interactions. These patients are likely to develop kidney injury, which may be transitory or not. However, those exposed by a prolonged use of drugs are those with chronic kidney disease, with a 3 to 4-fold increase in risks of adverse effects [3, 5-7].

Approximately 1%-5% of patients exposed to nonsteroidal anti-inflammatory drugs (NSAIDs) develop diverse nephrotoxic syndromes warranting potential physician intervention. Whereas, on the surface, this relatively low prevalence is not alarming, the extensive use profile of these analgesic, anti-inflammatory, and antipyretic agents implies that an enormous number of US citizens is at risk for consequential kidney dysfunction. For instance, approximately 1 in 7 patients with rheumatologic disorders is likely to receive such a prescription, and approximately 1 in 5 (50 million) US citizens report they use an NSAID for other acute complaints; thus, it is possible to estimate that some type of renal abnormality is likely to develop among the 500,000 to 2.5 million US citizens exposed to NSAIDs on a regular or intermittent basis per annum. The problem takes on added dimensions in that 20% of NSAID patients at risk are predisposed to the development of renal toxicity because of volume-contracted states, low cardiac output, or other conditions tending to compromise renal perfusion. Use of NSAIDs may spiral upward with the aging of the US population and the attendant rise in chronic musculoskeletal disorders such as the arthritides [3, 8, 9].

Classification of NSAIDs

1. Non-selective COX inhibitors:

- Salicylates: Aspirin, sodium salicylate
- Propionic acid derivatives: Ibuprofen, naproxen, ketoprofen, flurbiprofen
- Anthranilic acid derivatives: Mefenamic acid, meclofenamic acid, flufenamic acid
- Aryl-acetic derivatives: Diclofenac, aceclofenac
- Oxicams: Piroxicam, tenoxicam, meloxicam
- Pyrolo-pyrol derivatives: Ketorolac
- Indole derivatives: Indomethacin
- Pyrozolone derivatives: Phenylbutazone, oxyphenbutazone

2. Preferential COX-2 inhibitors: Nimesulide, meloxicam, nabumetone

3. Selective COX-2 inhibitors: Celecoxib, rofecoxib, etoricoxib, parecoxib

4. Analgesics & anti-pyretics

- Para-amino phenol: Paracetamol
- Pyrozolone derivative: Metamizol, propiphenazone

Few trials use uniform diagnostic criteria for hepatotoxicity, and the incidence rate of adverse liver events is greatly dependent on such criteria, confounding attempts to compare data on the incidence of hepatotoxicity between trials on different NSAIDs [10]. Clinical trials that use routine monitoring of liver function have the highest likelihood of ascertainment of any liver function abnormalities, but the usefulness of these studies is often limited by small numbers of patients and limited exposure times, as hepatotoxicity may be asymptomatic. 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. Diclofenac, and particularly sulindac, are reported to be more commonly associated with hepatotoxicity. In one study, sulindac use was associated with a 5 to10 fold higher incidence of hepatic injury than other NSAIDS [11, 12].

Nephrotoxicity

Fortunately, NSAID-induced renal complications are typically fully reversible if the clinician suspects NSAID complications when presented with laboratory and histologic findings, and swiftly discontinues the offending NSAIDs. Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly prescribed medications and are responsible for upwards of 10% of all medications dispensed annually in the United States. One in every eight individuals currently reports taking an NSAID daily. The anti-inflammatory and analgesic effects of NSAIDs have been routinely utilized in clinical practice over the last seventy years. These agents are routinely administered for the myriad of conditions in which they are effective; including arthritis, fever, and pain. Furthermore, the over-the-counter availability and affordable cost of these agents lends to their ease of access [13-15].

Patients treated with NSAIDs may be at an increased risk for renal injury. NSAID-induced renal injury can present in various forms, resulting from either acute or chronic use. A correlation between NSAID-use and acute kidney injury (AKI) in an acute care setting is routinely encountered. Furthermore, studies have historically found that approximately five percent of patients initiated on NSAID therapy experience a kidney-related adverse event. In a prospective community-based study, elderly patients over the age of 66 were assessed for correlations between NSAID use and the progression of chronic kidney disease (CKD).

Progression to CKD was defined as a greater than 15mL/min decline in glomerular filtration rate using the Modification of Diet in Renal Disease (MDRD) equation formula. The MDRD equation accounts for age, race, sex, and serum creatinine. In this population, 26% of the total cohort developed CKD. The risk of injury can be observed with the use of either a non-selective cyclooxygenase inhibitor, such as naproxen and ibuprofen, or with a selective cyclooxygenase inhibitor, such as meloxicam or celecoxib. The risk of NSAID-induced AKI in various populations is 3.3%; however, a higher incidence appears to occur in individuals over the age of sixty, as well as in patients previously diagnosed with CKD. The adverse effects of NSAIDs contribute to a significant economic burden, both to the patient and to the healthcare system. AKI has been associated with increased length of hospitalization of 3.2 days with an associated cost of $7933 per incident.

Patients who experienced stage five CKD requiring renal replacement therapy (RRT), experienced an increased length of stay of 11.5 days, with an associated cost of $42 077 per incident. Therefore, strategies aiming to decrease the incidence of AKI may decrease overall healthcare expenditures and protect patients from unnecessary, avoidable risk (Figure 1) [16-19].

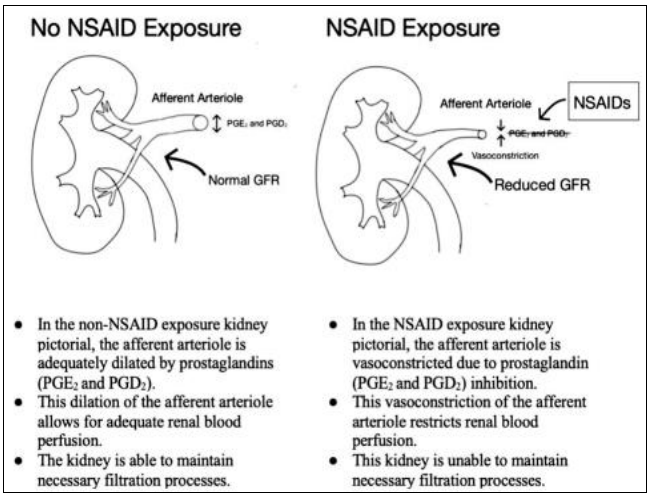

Fig 1: Mechanism of NSAID induced AKI

Mechanism of action of NSAIDs

NSAIDs inhibit cyclooxygenase (COX) which is also known as prostaglandin H synthase. There are two distinct isoforms of COX: COX-1 and COX-2. COX-1 is ubiquitous and constitutively expresses in normal cells. On the other hand, COX-2 is largely upregulated in inflammatory state. However, several studies have demonstrated an expression of COX-2 during normal state in several organs such as brain, reproductive organs and kidneys. The two isoforms of COX are 60% identical and located at luminal compartment of endoplasmic reticulum and nuclear membrane. NSAIDs bind with COX-1 via reversible hydrogen bond whereas the binding of COX-2 is an irreversible active process.

COX enzyme primarily involves in eicosanoid biosynthesis

which converts arachidonic acid to prostaglandin (PG) G_2. PGG_2 is then converted to PGH_2 via peroxidase enzyme. Ultimately, PGH_2 is metabolized to various types of PG including PGE_2, $PGF_{2\alpha}$, PGI_2 and thromboxane (TX) A_2 via isomerase enzymes (Figure 2). NSAIDs exert their anti-inflammatory property mainly via COX-2 inhibition whereas COX-1 inhibition often results in adverse effects. NSAIDs can be classified based on their COX-2 selectivity: non-selective COX inhibitors and selective COX-2 inhibitors. NSAIDs can also be classified based on their chemical structure and property such as carboxylic acids, acetic acids and propionic acids [20].

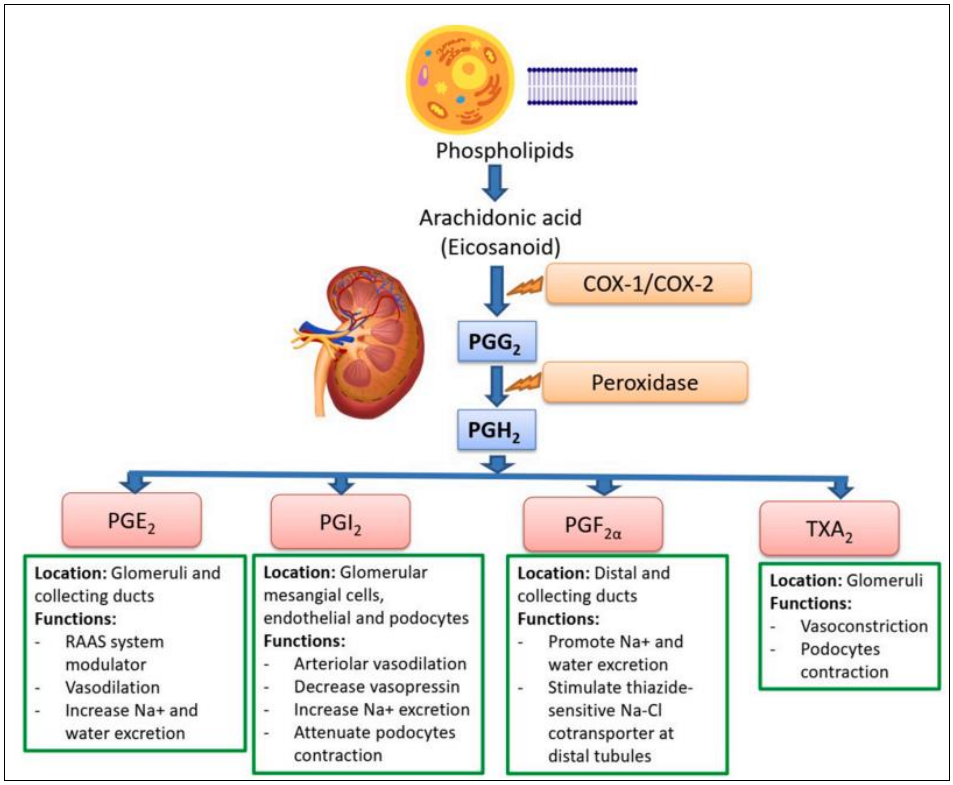

Fig 2: Prostaglandins production cascade, locations and their functions (PG-prostaglandin; TXA_2- thromboxane A_2)

Pathophysiology of NSAIDs-induced acute kidney injury

NSAIDs primarily incite AKI via hemodynamic alteration from prostaglandins imbalance. As previously mentioned, COX-1 is generally expressed in the kidneys during non-inflammatory state. Additionally, low level of COX-2 expression can be found in macula densa. PGs are expressed in several parts of nephron, including glomeruli, juxtaglomerular apparatus (JGA), loop of Henle, interstitial and tubular cells. Their function and site-specific expression help maintaining and modulating renal function (Figure 2).

PGI_2 (Prostacyclin) is up-regulated by vasoconstrictive hormones such as angiotensin II, vasopressin, endothelin and norepinephrine. Various injuries, including renal ischemia and autoimmune process in renal parenchyma, can stimulate PGI_2 production. Its receptors are located at glomerular mesangial cells, endothelial cells and podocytes. It enhances arteriolar vasodilation, decrease vasopressin and increase sodium excretion, thus promote diuresis. It can also attenuate podocytes contraction and inhibit leukocyte adhesion and aggregation.

PGE_2 is expressed in all type of renal cells but mostly in glomeruli and collecting ducts. There are three types of PGE_2 synthase, including microsomal PGE synthase (mPGES)-1, mPGEs-2 and cytosolic PGE synthase. PGE_2 binds to EP receptor which has 4 subtypes (EP_1-EP_4). EP_1/EP_3 act as vasoconstrictor whereas EP_2/EP_4 act as vasodilator of afferent arterioles. EP_2/EP_4 also serve as vasodilator for vasa recta. It is a mediator of renin-angiotensin aldosterone synthesis (RAAS) that can stimulates renin release via EP_3 from the macula densa. Overall, PGE_2 promotes vasodilation, natriuresis and aquaresis [21].

TXA_2 is widely expressed and can be found in macrophages, lung, peritoneum and kidneys. Expression of TXA_2 particularly abundant in platelet which promotes platelet activation and aggregation. In the kidneys, TXA_2 is primarily expressed in glomeruli. It promotes vasoconstriction and podocytes contraction, thus decrease renal blood flow and glomerular filtration (GFR). $PGF_{2\alpha}$ is converted from PGD_2 via 11-ketoreductase. It is highly expressed along genitourinary tract, including ovaries and kidneys. Distal convoluted tubule and cortical collecting duct are the main sites of renal expression. It promotes sodium and water excretion via transcellular transport of sodium independently of blood pressure and GFR. It also stimulates thiazide-sensitive Na^+ Cl^- cotransporter in distal convoluted tubule.

NSAIDs deplete locally produced PGs in the kidneys and, thus, blunt vasodilatory and other compensatory effects. These effects are especially crucial for high-risk patients who already have up-regulated RAAS and vasoconstrictive mediators [endothelin-1 (ET-1) and norepinephrine] as they are dependent on vasodilation properties of PGs to maintain normal renal hemodynamics. PGI_2 and PGE_2 are the main vasodilators. PGI_2 enhances afferent, efferent and capillary tuft dilatation. PGE_2 also dilates afferent arterioles. Removal of vasodilators can impose unopposed severe renal vasoconstriction. Ultimately, this may lead to irreversible

renal ischemia and acute tubular necrosis. Several animal studies have shown that prostacyclin reduction increases risk of ischemic kidney injury and endothelial PGs could protect kidneys from ischemic insult. These studies confirm the inhibitory role of NSAIDs in PGs production leading to ischemic injury (Figure 3).

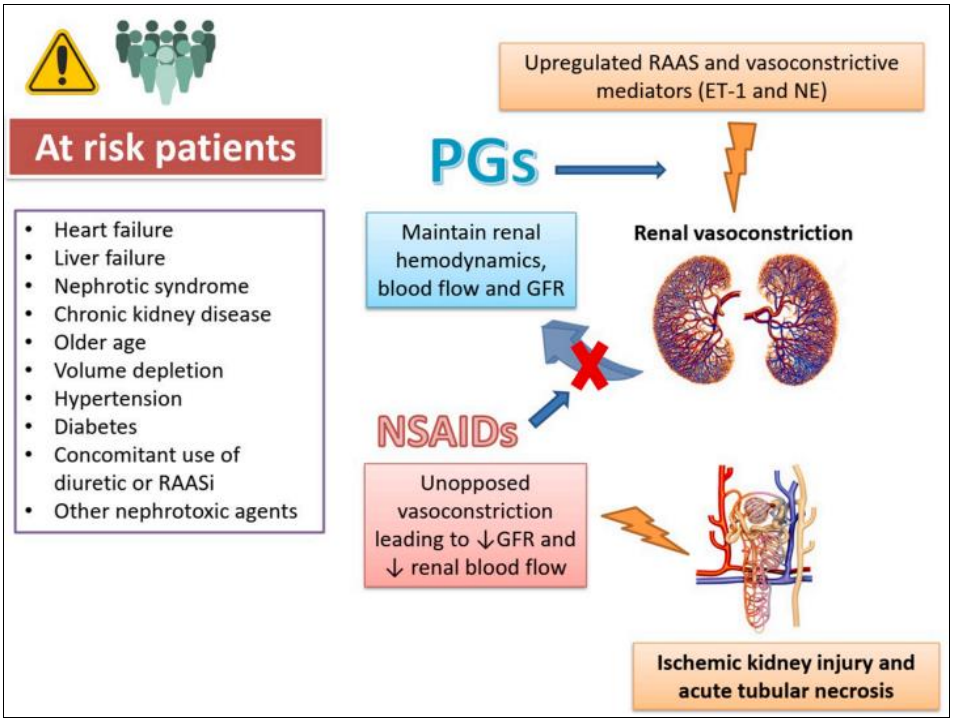

Fig 3: Risk factors of NSAIDs induced nephrotoxicity and mechanism of acute kidney injury. Abbreviations: RAASi, renin angiotensin aldosterone system inhibitor; PGs, prostaglandins; NSAIDs, nonsteroidal anti-inflammatory drugs; ET-1, endothelian-1; NE, norepinephrine

Clinical presentation

Renal manifestation of NSAIDs is protean, including fluid retention leading to edema, hypertension, hyperkalemia, AKI, nephrotic syndrome, papillary necrosis and interstitial nephritis. Clinicians should be aware of these manifestations and promptly ask for history NSAIDs exposure. These manifestations are demonstrated in Figure 4 [5, 21-25].

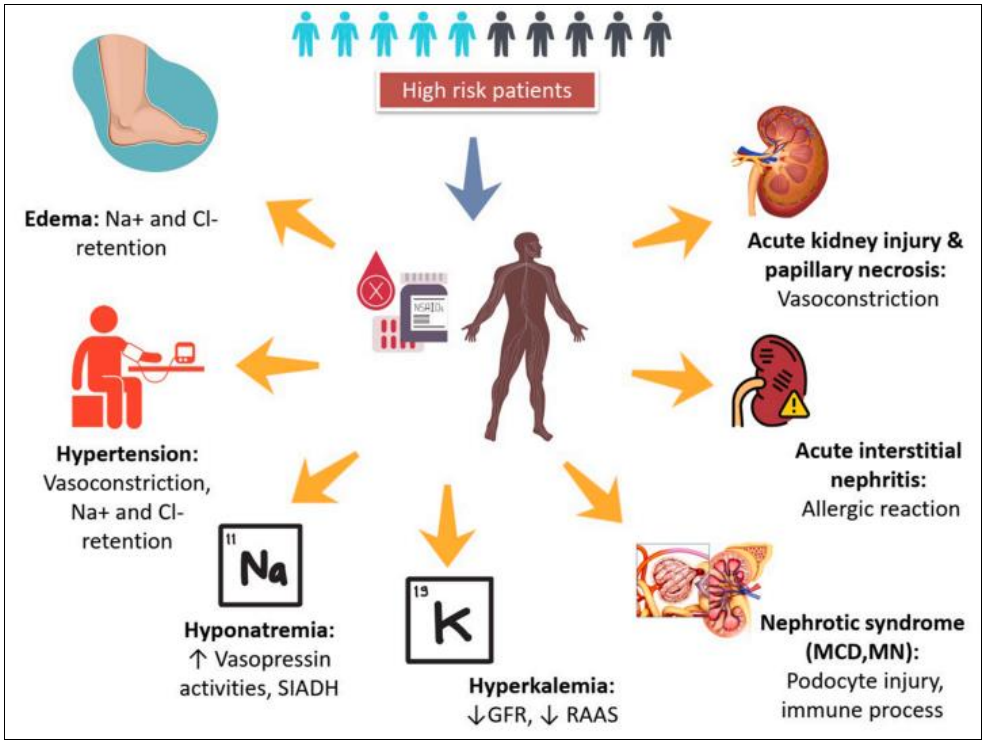

Fig 4: Spectrum of NSAIDs induced nephrotoxicity. Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; SIADH, syndrome of inappropriate anti-diuretic hormone; GFR, glomerular filtration rate; RAAS, renin angiotensin aldosterone system; MCD, minimal change disease; MN, membranous nephropathy

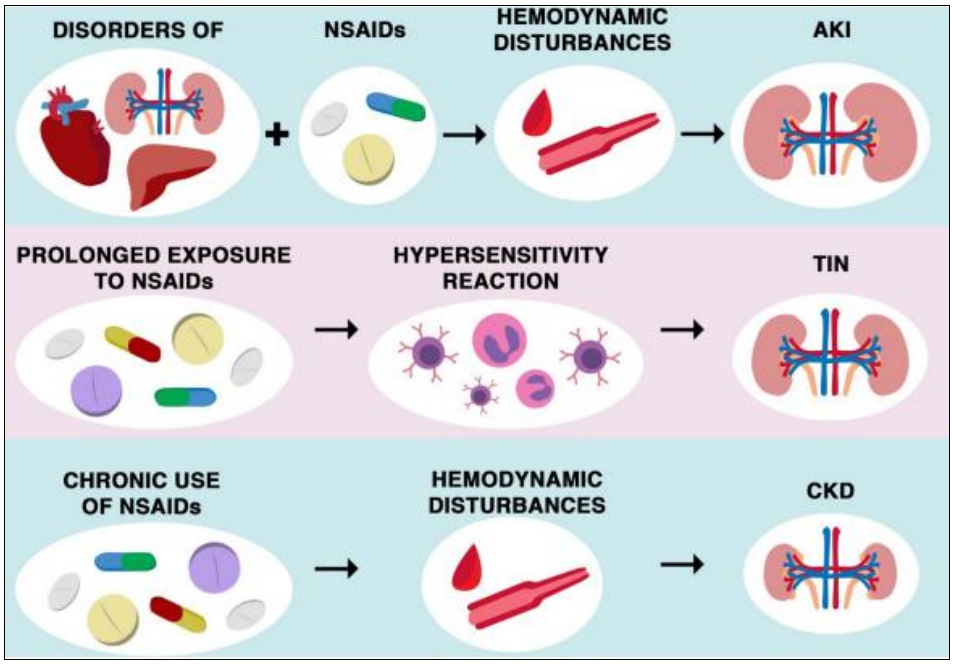

Fig 5: Summarization of main renal pathomechanisms associated with NSAIDs usage. The usage of NSAIDs could disturb kidney function in multiple pathways. The chronic usage of NSAIDs could lead to CKD as the effect of hemodynamic disturbances. The TIN could be the effect of the consequence of prolonged exposure to NSAIDs. A possible mechanism is assigned to a delayed hypersensitivity reaction, with interstitial infiltration of eosinophils and T cells. NSAIDs could also lead to AKI, especially in patients with comorbidities and polypragmasia. (AKI, acute kidney injury; CKD, chronic kidney disease; NSAID, nonsteroidal anti-inflammatory drugs; TIN, tubulointerstitial nephritis)

Hepatotoxicity

Liver is the only organ, and only found in vertebrates which performs many essential biological functions such as detoxification, metabolism of drugs through enzyme activation, metabolism of fats, proteins & carbohydrates, bile production & excretion, storage of vitamins and synthesis of proteins like albumin & clotting factors. Now how liver involved in metabolism of drugs is usually after absorption of drugs it undergoes first pass metabolism where they activated or inactivated by liver enzymes. Metabolism is two types; phase I & phase II. Phase I is carried through this CYP family and phase II involves microsomal enzymes like glucuronidation, sulfation methylation, drugs undergo metabolism and turns out in to polar substances to ease elimination. Some drugs are activated here called prodrugs, so liver performs many functions damage to liver will interrupt this or halt these functions [26]. Majorly drugs effect this organ if used high dosed with more frequency or drugs with action consumed or boozing very frequently. How drugs injure the liver is there are many mechanisms, where drugs induce injury stimulation of autoimmunity, idiosyncratic reaction, stimulation of apoptosis, mitochondrial injury, metabolic activation of CYP enzymes, disruption of Ca^{+2} homeostasis and cell membrane injury [27, 28].

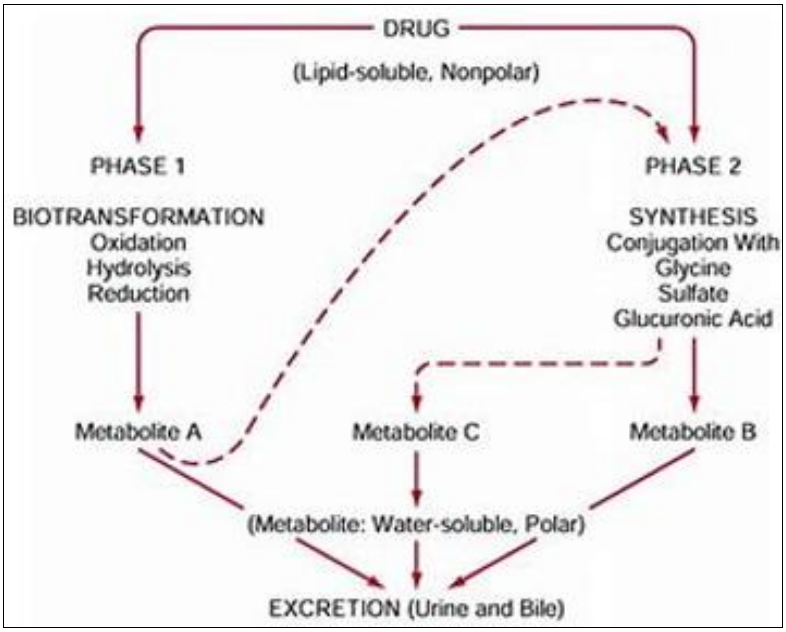

Fig 6: Kinetics of a drug

Fig 7: Liver injury

Nonsteroidal anti-inflammatory drugs (NSAIDs) belong to a group of chemically heterogeneous compounds, and their therapeutic effect relies on the strong anti-cyclooxygenase activity and ability to block pro-inflammatory substance formation. The main indications for NSAID therapy range from mild/moderate forms of pain to chronic inflammatory processes.

In the United States, 6% of the population declared taking at least one prescription NSAID a month, and over 30 million people around the world take NSAIDs daily. Conventional NSAIDs are generally well tolerated, but adverse effects such as cardiovascular, gastrointestinal and renal events may occur in a small proportion of users. NSAID-associated hepatotoxicity is considered rare and the incidence is estimated to be 1-23 cases per 100,000 patient-years. In addition, previous systematic reviews have found low level of liver-related hospitalisation involving NSAID intake. Nevertheless, the common use of NSAIDs emphasises the importance of understanding NSAID-associated liver toxicity, which is responsible for approximately 10% of drug-induced liver injury (DILI) cases in developed countries [29-31].

Interestingly reports from prospective DILI cohorts around the world demonstrate differences in relative frequency of individual NSAIDs responsible for DILI. Diclofenac was the most common causative NSAID in the United States (63%) and Iceland (100%), while nimesulide more frequently caused DILI in Latin America (38%) and Italy (39%). 10-13 Ibuprofen, on the other hand, was the NSAID responsible for most DILI cases in the Spanish DILI Registry (29%) and was also highly represented in an Indian DILI study (25%), although the latter study presented a more equal distribution between different NSAIDs than the former study. Caution should however be taken when interpreting these results due to lack of sales/prescription data.

Hepatotoxicity is more frequently discovered during post marketing studies or, even, much later. This is due to the slightly low incidence rate of NSAIDs associated with hepatotoxicity. The sample size of the premarketing studies designed to assess the efficacy or safety of NSAIDs might not be sufficient to provide the true incidence rate of hepatotoxicity. Although clinically apparent liver injury from NSAIDs is rare (~1–10 cases per 100,000 prescriptions), NSAIDs are consumed in massive amounts worldwide; hence, despite the overall low incidence rate of NSAID induced hepatotoxicity, their widespread use makes them an important cause of drug-induced liver injury [31-34].

Clinical features of hepatotoxicity due to NSAIDs

Hepatotoxicity from NSAIDs can occur at any time after drug administration, but like most adverse drug reactions, most commonly occurs within 6–12 weeks of initiation of therapy. In one series of 180 patients with diclofenac related hepatotoxicity, 33% were detected as a result of routine laboratory analyses and 67% were detected by symptoms (of these 67% were jaundiced); 79% were female and 71% were over 60 years of age. Hepatic injury was apparent by 1 month after starting the drug in 24%, by 3 months in 63%, and by 6 months in 85% of cases. Acute liver failure occurs in a tiny proportion of individuals exposed and is often not recognized as a possible adverse event until the post-marketing stage [35].

There are two main clinical patterns of hepatotoxicity due to NSAIDs. The first is an acute hepatitis with jaundice, fever, nausea, greatly elevated transaminases and sometimes eosinophilia. The alternative pattern is with serological (ANF-positive) and histological (periportal inflammation with plasma and lymphocyte infiltration and fibrosis extending into the lobule) features of chronic active hepatitis. In one series of 44 patients with drug-induced hepatotoxicity, three (7%) presented with hepatic failure, (54%) presented with jaundice, and (39%) were asymptomatic and were picked up because of abnormal liver function tests performed as part of routine investigations. At follow-up at a median of 5 years later, eight had persistently abnormal liver function tests, although in another series (as in our clinical experience) liver function test abnormalities generally resolved within 4–8 weeks of discontinuing the causative drug. One of the patients in this latter series died from acute liver failure, and there are many other isolated case reports of NSAID-related acute liver failure leading to liver transplantation or death [36].

Mechanism of hepatotoxicity of NSAIDs

Two main mechanisms are responsible for injury: hypersensitivity and metabolic aberration. Reported risk factors for NSAID-induced idiosyncratic hepatotoxicity include female sex, age >50 years and underlying autoimmune disease. However, whether these are true risk factors or merely represent the population taking NSAIDs, remains to be established. In one retrospective cohort study, NSAID users with rheumatoid arthritis had a ten-fold increased risk of NSAID-related hepatotoxicity when compared with NSAID-users with osteoarthritis. Another risk factor is concomitant exposure to other hepatotoxic drugs. Patients who have experienced hepatotoxicity to one

NSAID, often have the same reaction if the drug is restarted or a sister drug is given, particularly if the sister drug is structurally similar, e.g., diclofenac and tiaprofenic acid. Hypersensitivity reactions often have significant anti-nuclear factor or anti-smooth muscle antibody titres, lymphadenopathy and eosinophilia. Rechallenge with the drug results in a repeat increase in anti-nuclear factor titres. A recent rechallenge from an error caused by generic and non-generic prescribing of diclofenac resulted in a liver transplantation for one patient.

Background

NSAIDS are indicated in the treatment of various acute and chronic inflammatory conditions, headaches, and fever. The pharmacologic properties of the various NSAIDS are related to their molecular structure, which can be categorized into the five classes. Not all of these listed agents are currently available either in the United States or elsewhere. Only ibuprofen and naproxen are available over-the-counter (in the United States); the rest are by prescription only. Carprofen and phenylbutazone are available in the United States as veterinary medications. NSAIDs withdrawn from use or testing because of hepatotoxicity or other serious adverse events include benoxaprofen, sudoxicam, isoxicam, fluproquazone, bromfenac, oxyphenbutazone and phenylbutazone (aplastic anemia), indoprofen (gastrointestinal bleeding), suprofen and zomepirac (anaphylaxis). NSAIDs in use in other countries of the World include acemetacin, azaproprazone, fenbufen, feprazone, floctafenine, flufenamic acid, nimesulide, pirprofen, and tiaprofenic acid.

Aspirin and acetaminophen are technically NSAIDs and they can cause liver injury, but the injury is due to intrinsic toxicity and usually associated with use of high doses or overdoses. For this reason, aspirin and acetaminophen are discussed separately. The liver injury caused by typical NSAIDs is, in contrast, most likely idiosyncratic. Clinically apparent liver injury from NSAIDs is rare (~1-10 cases per 100,000 prescriptions) and typically presents as acute hepatitis within 1 to 3 months of starting the medication. Cases of fatal hepatitis tend to present much later - after 12 to 15 months. Sulindac and diclofenac are the NSAIDs that are most commonly linked to hepatotoxicity, but virtually all NSAIDs that have been used extensively have been linked to at least rare cases of clinically apparent drug induced liver injury. The pattern of injury is mainly hepatocellular, although cases of cholestatic (sulindac, ibuprofen), and mixed (naproxen) injury have been reported. Typical presenting symptoms include fever, malaise, jaundice and itching. The clinical pattern may depend on the pattern of injury. Hepatocellular injury presents with marked serum aminotransferase elevations, fatigue and jaundice, while cholestatic injury presents with jaundice and itching with marked elevations in alkaline phosphatase and bilirubin levels. Histology varies greatly. Women and the elderly, as well as patients with chronic hepatitis C may be more susceptible.

In addition to the clinically apparent, idiosyncratic liver injury due to NSAIDs, transient, mild and asymptomatic elevations in serum aminotransferase levels occur in up to 18% of patients taking NSAIDs over a prolonged period. The rate of such aminotransferase abnormalities varies by the different NSAIDs, but the rate is highly dependent upon the rigor with which such elevations are sought (whether by regular monitoring at frequent intervals or irregularly and only occasionally during long term use) and the level of abnormality that is reported (any value above the upper limit of the normal range or values that are twice or three-fold elevated). The rate of aminotransferase elevations is also dependent upon the population studied, tending to be more common in obese patients and patients with serious underlying disease. Nevertheless, these minor elevations associated with NSAID use are usually self-limited, not accompanied by symptoms and rapidly resolve even if the medication is continued. In some studies, the rates of serum aminotransferase elevations are no higher than occurs in placebo recipients, raising some doubt as to the association of these changes with NSAID use.

Mechanism of injury

The apparent mechanism by which almost all NSAIDs produce hepatic injury is idiosyncrasy rather than intrinsic toxicity. The main exceptions to this are acetaminophen and aspirin, in which case a dose related injury. Although many cases of NSAIDs related liver injury demonstrate evidence of an immunologic cause, there is evidence that toxic metabolites contribute to the liver injury for some NSAIDs [37].

Indomethacin and ibuprofen

Indomethacin may disrupt the protective effects of FXR (Farnesoid X receptor) through the activation of $STAT_3$ phosphorylation in $HepG_2$ cells, a study has shown. It has also been reported that liver injury could lead to the signal transducer and activator of transcription 3 ($STAT_3$) phosphorylated and inhibit/recessive $STAT_3$ activation. The transient transfection assays show that seven drugs with inhibition rates larger than 60% in yeast two-hybrid display excellent antagonistic activity against FXR. ibuprofen is more potent than GS and decreases transcriptional activity on FXR induced by chenodeoxycholic acid (CDCA). In $HepG_2$ cells, indomethacin and ibuprofen stimulate FXR target genes. The two most potent antagonists (indomethacin and ibuprofen) were used to further investigate the NSAIDs' FXR antagonistic activities to examine their effects on the expression of genes targeted by CDCA in an FXR-dependent way. $HepG_2$ cells were cultured in the laboratory using varying ratios of indomethacin and ibuprofen for 24 h.

Aspirin

Aspirin is the drug, which inhibits the COX irreversibly. Liver toxicity induced by aspirin is considered to be dose-dependent; but there is evidence that rheumatic patients may have predisposing conditions that may increase individual risk of liver damage. Aspirin causes a mitochondrial dysfunction that may lead to a liver free/fatty acid accumulation and subsequently develop into a metabolic disorder associated with hepatic massive steatosis. And depletion of carnitine and acyl-coenzyme & increase urea levels. Usually, aspirin causes this in children's and they develop hypertension now it has been replaced with many other NSAIDs [37, 38].

Diclofenac

The most commonly used NSAID worldwide is diclofenac. Retrospective studies account for the great majority of information on hepatic responses. In 1995, there were only

60 cases of diclofenac hepatotoxicity mentioned in the literature. Within the first six months following medication ingestion, the investigators found signs of liver damage in 85% of the patients. Curiously, 12% of cases showed a higher latency (after 6 months). A metabolic mechanism of hepatotoxicity is supported by the prolonged latency time seen in many cases and the absence of hyper-sensibility. In 90 out of 120 cases, jaundice was a fairly prevalent symptom. The combination of mechanisms that cause hepatotoxicity, such as drug metabolism, reactive metabolite production, and clearance, determine the actual onset and extent of liver damage. Diclofenac is a prominent example of this. Additionally, diclofenac may cause liver damage e either through an immunological mechanism produced by the production of drug addicts or through a metabolic abnormality. Furthermore, diclofenac is more cytotoxic to drug-metabolizing cells than non-metabolizing cell lines ($HepG_2$). Impaired ATP synthesis by mitochondria and affects drug metabolism and is reduced by supplementation of cytochrome P450 inhibitors.

Coxib

The mechanism of coxib-induced liver injury remains to be elucidated. Bioactivation of lumiracoxib and its metabolite [4'-Hydroxymiracoxib (M_5), growth stimulating hormone depletion, covalent binding to proteins and oxidation stress can lead to liver damage. Still, hepatotoxicity caused by non-selectivity NSAIDs need to be studied more extensively. Aside from that, mitochondrial damage, cholestasis and oxidative stress induced by the formation of reactive metabolites are the most prominent molecularly reported disorder. A hypothesis suggests that NSAIDs inhibit the inhibition of: COX-2 can cause liver damage via prostaglandins (PG) Method. Related to this concept, the authors suggested that inhibition of PGE_2 could be downregulated. Anti-apoptotic mitochondrial protein Bcl-2 that protects against bile acid-induced apoptosis.

Oxicam and nimesulide

Piroxicam induced severe hepatocellular necrosis was the most frequent reported clinical pattern with recovery, death and need of liver transplantation difficult to occur. It is yet unknown how nimesulide causes hepatotoxicity. It has been proposed that it might result from the production of a reactive metabolite. On the other hand, it has also been suggested that medication metabolism may vary depending on an individual's genetic makeup. It is difficult to fully comprehend how nimesulide affects the liver. Despite the abundance of reports describing nimesulide-induced severe liver injury (mostly from Argentina, Ireland, and Finland), epidemiological studies almost always came to the conclusion that severe hepatotoxicity is rare, resulting in a favourable risk-benefit ratio. Standard liver disease anamnesis should include a question about nimesulide intake, especially when looking into acute liver damage [34, 39, 40].

Conclusion

Our findings suggest that NSAID induced AKI is a complex process that has wide inter patient variability. The mechanism of injury varies based on acute or chronic use of NSAIDs. The presentation of disease differs depending on patient-specific risk factors, such as volume depletion, comorbid conditions, use of high-risk medications, or concomitant diagnostic contrast dye. Healthcare providers' understanding of the pathophysiology, diagnostic criteria, and risk factors associated with AKI is vitally important to improve clinical outcomes. Proactively screening high risk patients and utilizing appropriate mitigation strategies, such as adequately hydrating patients and limiting NSAID exposure to the lowest dose for the shortest period of time. As illustrated by the case vignette, AKI can be precipitated through the use of a typical NSAID regimen, demonstrating the importance of proper risk factor management. Practitioners should also limit use of NSAIDs in patients with cardiovascular disease or in patients undergoing diagnostic evaluation with contrast dyes. Implementation of risk mitigation strategies and educational strategies targeting healthcare professionals has the potential to decrease negative clinical and economic outcomes. In summary, to report liver safety assessment from randomized controlled trials, the requirements for the studies should be uniform; for example, necessary criteria such as precise definitions and report outcome should be clearly specified. To minimize potential risk of hepatotoxicity from NSAIDs, especially diclofenac, the lowest effective dose is recommended and avoid dispensing those NSAIDs as the first-line drug if other safer NSAIDs are available.

Disclosure

The authors declare no conflict of interest.

References

1. Onder G, Pellicciotti F, Gambassi G, Bernabei R. NSAID-related psychiatric adverse events: who is at risk? Drugs,2004:64(23):2619–2627.
2. Dubois RN, Abramson SB, Crofford L, *et al*. Cyclooxygenase in biology and disease. Faseb J,1998:12(12):1063–1073.
3. Wongrakpanich S, Wongrakpanich A, Melhado K, Rangaswami J. A comprehensive review of non-steroidal anti-inflammatory drug use in the elderly. Aging Dis,2018:9(1):143–150.
4. Cui Y, Yang Y, Lei W, Lang X, Chen J. The clinicopathological features of drug induced acute kidney injury-a single-center retrospective analysis. Ann Transl Med,2021:9(5):400.
5. Whelton A, Hamilton CW. Nonsteroidal anti-inflammatory drugs: effects on kidney function. J Clin Pharmacol,1991:31(7):588–598.
6. Baker M, Perazella MA. NSAIDs in CKD: are they safe? American J Kidney Dis,2020:76(4):546–557.
7. Bouck Z, Mecredy GC, Ivers NM, *et al*. Frequency and associations of prescription nonsteroidal anti-inflammatory drug use among patients with a musculoskeletal disorder and hypertension, heart failure, or chronic kidney disease. JAMA Internal Med,2018:178(11):1516–1525.
8. Jeong R, Lentine KL, Quinn RR, *et al*. NSAID prescriptions in kidney transplant recipients. Clin Transplant,2021:35(9):e14405.
9. Hla T, Bishop-Bailey D, Liu CH, Schaefers HJ, Trifan OC. Cyclooxygenase-1 and -2 isoenzymes. Int J Biochem Cell Biol,1999:31(5):551–557.
10. Cashman JN. The mechanisms of action of NSAIDs in analgesia. Drug,1996:52(5):13–23.
11. Zarghi A, Arfaei S. Selective COX-2 inhibitors: a review of their structure-activity relationships. Iran J Pharm Res,2011:10(4):655–683.

12. Hawkey CJ. COX-1, COX-2 inhibitors. Best Pract Res Clin Gastroenterol,2001:15(5):801–820.
13. Han Y, Balkrishnan R, Hirth RA, *et al*. Assessment of prescription analgesic use in older adults with and without chronic kidney disease and outcomes. JAMA Netw Open,2020:3(9):e2016839.
14. Drozdzal S, Lechowicz K, Szostak B, *et al*. Kidney damage from nonsteroidal anti-inflammatory drugs-Myth or truth? Review of selected literature. Pharmacol Res Perspect,2021:9:e00817.
15. Wong K, Cha B, Wu S. Case of ibuprofen-induced liver injury. AIM Clinical Cases,2023:2:e220880.
16. Blackshear H, Napier JS, Davidman M, Stillman MT. Renal complications of nonsteroidal anti-inflammatory drugs; identification and monitoring of those at risk. Semin. Arthritis Rheum,1985:14:163–175.
17. Chiu HY, Huang HL, Li CH, Chen HA, Yeh CL, Chiu SH, et al. Increased Risk of Chronic Kidney Disease in Rheumatoid Arthritis Associated with Cardiovascular Complications-A National Population-Based Cohort Study. PLoS One,2015:10:e0136508.
18. Cho E, Curhan G, Hankinson SE, *et al*. Prospective evaluation of analgesic use and risk of renal cell cancer. Arch Intern Med,2011:171(16):1487–1493.
19. Choueiri TK, Je Y, Cho E. Analgesic use and the risk of kidney cancer: a meta-analysis of epidemiologic studies. Int J Cancer,2014:134(2):384–396.
20. Ornbjerg LM, Andersen HB, Kryger P, Cleal B. What do patients in rheumatologic care know about the risks of NSAIDs? *J Clin Rheumatol: practical reports on rheumatic & musculoskeletal diseases*,2008:14(2):69–73.
21. Shah S, Mehta V. Controversies and advances in non-steroidal anti-inflammatory drug (NSAID) analgesia in chronic pain management. *Postgraduate Medical Journal*,2012:88(1036):73–78.
22. Weir MR. Renal effects of nonselective NSAIDs and coxibs. Cleve Clin J Med,2002:69(Suppl1):SI69–SI76.
23. Rani Samyuktha Velamakanni, Sai Kishore Pittla, Srikanth Reddy Anugu, Raj Kiran Sriramula, Mounika Tejaswi Gorle, Narender Boggula. *Efficacy of anti-hypertensives in prolonging diabetic nephropathy. International Journal of Research in Pharmacy and Chemistry,2018:(3):422-436.*
24. Moore N, Charlesworth A, Van Ganse E. Risk factors for adverse events in analgesic drug users: results from the PAIN study. Pharmacoepidemiol Drug Saf,2003:12(7):601–610.
25. Farquhar WB, Morgan AL, Zambraski EJ, Kenney WL. Effects of acetaminophen and ibuprofen on renal function in the stressed kidney. J Appl Physiol,1999:86(2):598–604.
26. Aithal GP, Day CP. Nonsteroidal anti-inflammatory drug-induced hepatotoxicity. *Clinics in Liver Disease*,2007:1(3):563–575.
27. Bessone F. Non-steroidal anti-inflammatory drugs: What is the actual risk of liver damage? *World Journal of Gastroenterology*,2010:16(45):5651–5661.
28. Sarges P, Steinberg JM, Lewis JH. Drug-induced liver injury: highlights from a review of the 2015 literature. *Drug Safety*,2016:39(9):801–821.
29. Kaplowitz N. Rules and laws of drug hepatotoxicity. *Pharmacoepidemiology and Drug Safety*,2006:15(4):231–233.
30. Jahnavi K, Pavani Reddy P, Vasudha B, Narender B. Non-steroidal anti-inflammatory drugs: an overview. Journal of Drug Delivery and Therapeutics,2019:9(1-s):442-448.
31. Shahnazarian V, Ramai D, Reddy M. A rare case of ibuprofen-induced acute liver injury. Cureus,2018:10:e3225.
32. Zoubek ME, Lucena MI, Andrade RJ, Stephens C. Systematic review: ibuprofen-induced liver injury. Aliment Pharmacol Ther,2020:00:1–9.
33. Purdum PP 3rd, Shelden SL, Boyd JW, Shiffman ML. Oxaprozin-induced fulminant hepatitis. Ann Pharmacother,1994:28:1159–1161.
34. Y Zhou, DM Boudreau, AN. Freedman. Trends in the use of aspirin and nonsteroidal anti-inflammatory drugs in the general U.S. population. Pharmacoepidemiology and Drug Safety,2014:23(1):43–50.
35. Zimmerman HJ. The NSAIDs. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, 517-41.
36. Grossner T, Smyth EM, Fitzgerald GA. Pharmacology of inflammation, fever, pain, and gout. In, Brunton LL, Hilal-Dandan R, Knollman BC. Goodman & Gilman's The pharmacological basis of therapeutics, 13th ed. New York: McGraw-Hill, 2018, 685-709.
37. Cuthbert MF. Adverse reactions to non-steroidal antirheumatic drugs. Curr Med Res Opin,1974:2:600–610.
38. Nachimuthu S, Volfinzon L, Gopal L. Acute hepatocellular and cholestatic injury in a patient taking celecoxib. *Postgraduate Medical Journal*,2001:77(910):548–550.
39. Kaplowitz N. Rules and laws of drug hepatotoxicity. *Pharmacoepidemiology and Drug Safety*,2006:15(4):231–233.
40. Grieco A, Miele L, Giorgi A, Civello IM, Gasbarrini G. Acute cholestatic hepatitis associated with celecoxib. *Annals of Pharmacotherapy*,2002:36(12):1887–1889.