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Review Article

Non- Selective Cox Inhibitor NSAID's Induced Nephropathy: A Systematic Review

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ABSTRACT

Non-Steroidal Anti-Inflammatory Drugs or NSAIDs are commonly used for their anti-inflammatory, analgesic, and antipyretic properties. NSAIDs can be classified as nonselective or selective based on their ability to inhibit different forms of the cyclooxygenase (COX) enzyme. Nonselective NSAIDs inhibit both COX-1 and COX-2 enzymes, while selective NSAIDs primarily inhibit COX-2, which is involved in inflammation. Common nonselective NSAIDs include ibuprofen, diclofenac, and naproxen. By blocking the enzyme, NSAIDs reduce the production of inflammatory mediators' prostaglandins and thromboxane. However, this inhibition can also affect kidney function by interfering with arachidonic acid metabolism leading to fluid and electrolyte retention. The development of NSAID-related nephrotoxicity is associated with multiple risk factors, such as systemic arterial hypertension, comorbidities, and advanced age. People who already have renal diseases, such as lupus nephritis, liver cirrhosis, nephrotic syndrome or heart failure, are also more vulnerable. Acute renal injury and acute interstitial nephritis can be the potential complications of NSAID use. Acute renal injury is characterized by a sudden decrease in GFR, leading to the retention of nitrogen waste products. Acute interstitial nephritis is characterized by inflammation and oedema in the renal interstitium. Overall, it provides a comprehensive review of the effects of nonselective COX inhibitor NSAIDs on kidney function, highlighting the potential nephrotoxicity and related risk factors.

INTRODUCTION

NSAIDs, or non-steroidal anti-inflammatory drugs, are among of the most used medications. Their anti-inflammatory, anti-pyretic, and analgesic properties make them an excellent therapeutic option for a variety of inflammatory conditions, including rheumatism and arthritis, as

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well as for ordinary pain relief.1 The history of Nonsteroidal anti-inflammatory medications, or NSAIDs begins long back when Hippocrates and other physicians prescribed willow bark for a variety of ailments. But when salicin (an alcoholic β-glucoside) was found to be the active component of willow plants, and acetylsalicylic acid was subsequently introduced by the Bayer Company some two centuries later, it laid the stage for the present era of NSAIDs.2 NSAIDs are classified as either nonselective or selective. COX-1 and COX-2 are the two main forms of Cyclooxygenase (COX) enzymes, and the terms nonselective and selective indicate how well an NSAID may inhibit each of these enzyme types.

- Nonselective NSAIDs - Nonselective NSAIDs inhibit both COX-1 and COX-2 enzymes to a significant degree.
- Selective NSAIDs - Compared to COX-1, which is typically found in the stomach, blood platelets, and blood arteries will inhibit COX-2, an enzyme present at sites of inflammation.3

Nowadays, nonselective NSAIDs like ibuprofen, piroxicam, mefenamic acid, diclofenac, naproxen, and selective NSAIDs that inhibit COX-2 such as celecoxib and rofecoxib are still staples in the treatment of pain and inflammatory disorders in addition to aspirin. 2 An inhibitory effect of NSAIDs is mostly seen on the enzyme cyclooxygenase (COX). Arachidonic acid cannot be converted into thromboxanes, prostaglandins, or prostacyclin without cyclooxygenase. The absence of these eicosanoids is thought to be responsible for the therapeutic benefits of NSAIDs.4 Kidneys are a special filter system in our body that removes waste products from the blood through urine and balances the levels of many substances in the blood such as salt, water, acids etc. and thus help to control blood pressure.5 NSAIDs can interfere in the normal functioning of Kidneys by altering the Arachidonic acid metabolism. The effect of NSAIDs in kidney depends on the dose, duration of use and the condition of the patient's renal functioning.6

MOA OF NSAIDs

The suppression of the cyclooxygenase (COX) enzyme is the primary mode of action of NSAIDs. Arachidonic acid must be converted by cyclooxygenase (COX) into thromboxanes, prostaglandins, and prostacyclins. It is thought that the absence of these eicosanoids is what gives NSAIDs their therapeutic benefits. In particular, prostaglandins induce vasodilation, raise the hypothalamic temperature set-point, and contribute to anti-nociception, while thromboxanes are involved in platelet adhesion.7 There are COX-1 and COX-2, two isoenzymes of cyclooxygenase. In addition to its role in maintaining renal afferent arteriole vasodilation, platelet aggregation, and the mucosa lining in gastrointestinal tract, COX-1 is constitutively produced in the body. Inducible expression of COX-2 occurs during an inflammatory reaction, rather than constitutively in the body. The majority of NSAIDs are non-selective because they block both COX-1 and COX-2.8

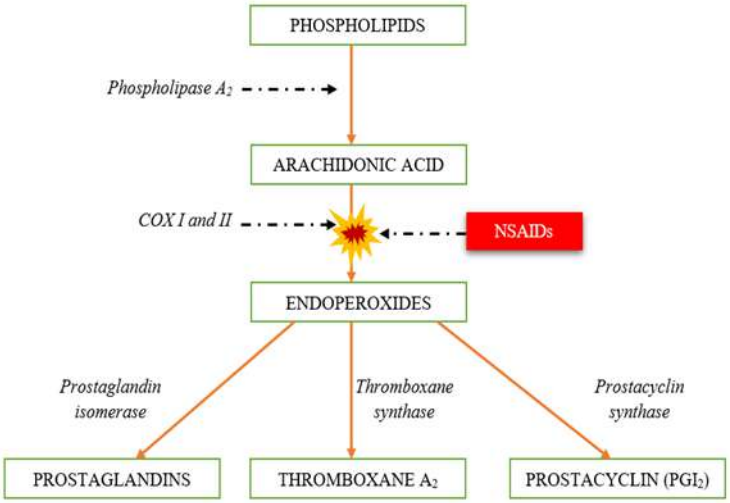

Fig 01: General MOA of NSAIDs27

PATHOPHYSIOLOGY OF NSAID KIDNEY INJURY

The kidneys are important organs for the excretory function of the body because they receive about 25% of all cardiac output.9 These organs have regulatory mechanisms, like prostaglandin production, that maintain renal homeostasis and glomerular filtration rate (GFR) so that they can effectively carry out their filtering role.10 When renal blood flow (RBF) needs to be increased, as it does when there is a decrease in GFR or effective circulation volume (ECV), COX plays a major role in increasing prostaglandin synthesis.11 NSAIDs either selectively or non-selectively block the arachidonic acid cycle, which prevents prostaglandin production. Prostaglandins, particularly prostacyclins, PGE2, and PGD2, spread cortical flow to the nephrons in the renal medullary portion of the kidneys by acting as vasodilators in the afferent arteriole and boosting renal perfusion.12 This vasodilatation results in compensation to guarantee appropriate flow to the organ by acting as negative feedback on the functions of the sympathetic nervous system and the renin-angiotensin-aldosterone system. NSAIDs suppress this process, which increases the risk of acute kidney damage by causing spinal cord ischemia and acute vasoconstriction.13 Activation of tubular receptors by triggering the EP1 receptor, PGE2 will block the movement of sodium and chloride to the collecting ducts and the ascending loop of Henle, resulting in natriuresis. Inhibiting PGE2 production may also result in increased sodium and water retention and the development of oedema, which is frequently subclinical. Thus, NSAID-induced COX-2 inhibition is probably a primary factor contributing to this medication class's nephrotoxicity.14 Apart from their effects on the kidneys, prostaglandins carry out various other homeostatic tasks including shielding the mucosa of the GI tract, stimulating platelets, causing inflammation, bronchodilation, and more.15 Figure illustrates the locations of prostaglandin action and COX-1 and COX-2 expression in human kidneys.

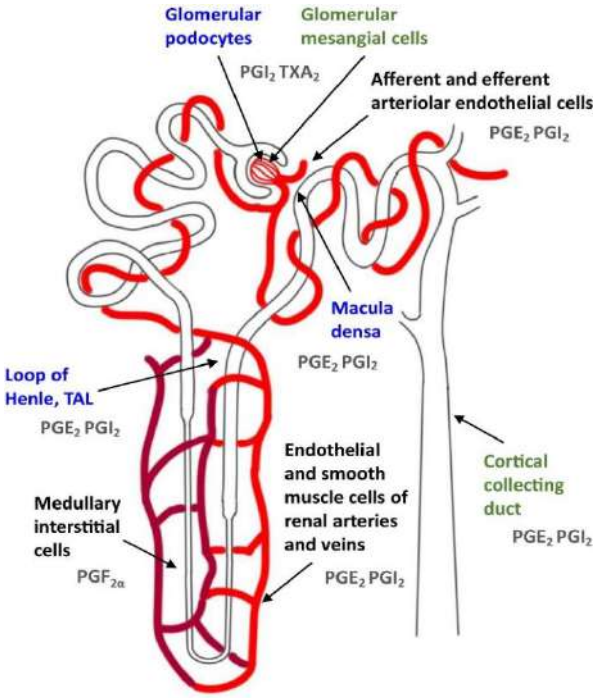

Fig 01: Locations of prostaglandin action and COX-1 and COX-2 expression in human kidneys.30

RISK FACTORS

It is uncommon for NSAID use to result in kidney damage, particularly in those who were previously healthy and did not abuse or take high doses of the medication. A number of variables, including advanced age and comorbidities, which by themselves cause a decline in GFR, raise the possibility of NSAID-related nephrotoxicity, which can exacerbate side effects.

Systemic arterial hypertension is one risk factor, which increases the activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system, causing vasoconstriction. Another risk factor is the inhibition of prostaglandin synthesis, which results in a suppression of the compensatory mechanism of renal vasodilation.16 Nephrotic syndrome with a high level of proteinuria, liver cirrhosis, heart failure and lupus nephritis may also contribute to renal damage.

NSAIDs AND ACUTE RENAL INJURY

The condition known as acute kidney injury is typified by a sudden decrease in GFR, which

causes the kidneys to retain nitrogen waste products such creatinine and urea. Clinical definitions of this syndrome include people who acquire oliguria/anuria, which justifies high morbidity and mortality in the emergency department, or who increase their creatinine levels within a few days (or if it is 1.5 times greater in relation to a recent or presumed outcome). Nearly every NSAID has a possible link to AKI.17 Hemodynamically mediated acute renal damage is the predominant kind brought on by NSAIDs. On the other hand, the production of these hormones rises to maintain renal perfusion and GFR in diseases such as hypovolemic shock, heart failure, liver failure, chronic kidney disease, and other illnesses that lower circulating arterial volume. Acute tubular necrosis (ATN) is more likely when NSAIDs interfere with this mechanism, decreasing intramedullary renal perfusion and ischemia.18

ACUTE INTERSTITIAL NEPHRITIS

Acute interstitial nephritis (AIN) is predominantly characterised by the development of oedema and inflammatory infiltrates within the interstitium, typically accompanied by an abrupt decline in renal function. There are a number of reasons why its actual incidence may be overestimated. Initially, a considerable proportion of patients with clinical suspicions of AIN are not subjected to a confirmation renal biopsy, as empirical treatment is deemed more appropriate, especially for older and weak individuals. Second, milder types of AIN may go undiagnosed because acute renal failure is mistakenly linked to other causes of renal damage or because clinical signs are absent or ambiguous.19 Drug-induced AIN is mainly caused by NSAIDs, antimicrobials and proton pump inhibitors.20 About 80% of patients have nephrotic proteinuria, which is most frequently linked to ibuprofen, naproxen, and phenoprofen. Although the precise processes underlying the pathophysiology of AINs induced by NSAIDs are unknown, a delayed hypersensitivity reaction has been proposed as the primary cause that indicate the following mechanisms: prolonged NSAID exposure required, low frequency of the traditional indications of hypersensitivity and an interstitial infiltration primarily composed of T cells.21

The destruction of basement membranes is one of the ways that NSAIDs harm the kidneys. The glomerular basement membrane thins, the slit pore diameter reduces, the density of podocytes decreases, and the mesangium grows when prolonged PG inhibition via NSAID use occurs. The patient's condition worsens as a result of those changes, and the illness advances faster. A disruption in the metabolism of arachidonic acid is also mentioned, which leads to the production of leukotrienes and their derivatives, which in turn stimulate T-lymphocytes and cause interstitial infiltration. This ultimately causes minimal lesion disease (MLD) to develop, along with nephrotic syndrome (oedema, oliguria, proteinuria) a few days after treatment commences. When medication is stopped, renal function normally returns.22

USE OF NSAIDS IN CKD

In the medical community, NSAIDs are thought to be detrimental to CKD patients. Presently, clinical guidelines advise against long-term NSAID usage in CKD with a GFR > 30 mL/min/1.73 m2 and total avoidance with a GFR < 30 mL/min/1.73 m2. The introduction of combination analgesics (NSAIDs combined with phenacetin, paracetamol, or salicylamide with caffeine or codeine) gave rise to concerns about NSAID-associated nephrotoxicity in patients with chronic kidney disease (CKD). These concerns are physiologically based on the idea that the "CKD kidney" lacks renal reserve.23, 24

A Cohort research by Chiu et al. published in 2015 found that NSAIDs, regardless of class or selectivity, increase the risk of nephrotoxicity in older individuals with chronic kidney disease (CKD) in a dosage-dependent manner. Of the over

12,000 people with comorbidities on NSAIDs, almost 10% saw a worsening of their kidney function. The result was statistically significant.25 Based on epidemiologic studies, persons with chronic kidney disease who use noncombination NSAIDs may be at higher risk for nephrotoxicity. On the other hand, comparing distinct populations that are identified by their NSAID use is a challenge faced by epidemiologic research looking at the risk for CKD progression from NSAIDs.26

Table 01: Major effects of NSAIDs on renal [21]

	Mechanisms	Risk factors	Prevention/Treatment
Water and Electrolyte disorders -Sodium retention -Hyperkalaemia -Hyponatremia -Metabolic acidosis -Lower response to diuretics (especially loop diuretics)	PGE2 and PG12-induced kidney vasodilatation inhibition; RAAS activation	NSAID use (most common nephrotoxic effects	Discontinue NSAID use
Acute Kidney Injury (AKI)	Hemodynamic alterations/ Kidney perfusion reduction	Liver diseases; kidney diseases; Heart failure; Dehydration; advanced age	Avoid in high-risk patients (patients with comorbidities); Discontinue NSAID
Acute Interstitial Nephritis (AIN)	Hypersensitivity reaction	Prolonged NSAID exposure; some specific NSAIDs (Phenoprofen, Naproxen, Ibuprofen)	Discontinue NSAID use
Chronic Kidney Disease (CKD)	Hemodynamic alterations	Chronic use of NSAIDS	Avoid use in high-risk patients (those with comorbidities and advanced age); Discontinue NSAID use
Papillary Necrosis	Direct toxicity	Phenacetine abuse; Aspirin and acetaminophen combination	Discontinue NSAID use and avoid chronic use of analgesics

PREVENTION AND MANAGEMENT

To reduce the risk of non-selective COX inhibitor-induced nephropathy, the following measures can be considered:

a. Avoiding High-Risk Patients: Individuals with pre-existing kidney disease or those at a higher risk of renal impairment should be cautious with NSAID use. Alternatives with a better renal safety profile, such as selective COX-2 inhibitors, may be considered.

b. Appropriate Dosing: NSAIDs should be prescribed at the lowest effective dose for the shortest possible duration to minimize the risk of renal injury.28

c. Monitoring: Regular monitoring of renal function, including serum creatinine and urine output, can help detect early signs of nephropathy in patients taking non-selective COX inhibitors.

d. Patient Education: Patients should be educated about the potential renal risks associated with NSAID use. They should be advised to report any symptoms of kidney injury promptly.2

CONCLUSION

Patients who are young, healthy, and free of concomitant conditions are not at significant risk when using NSAIDs. However, due to its dose-dependent impact, prolonged use of these medications should be done with extreme caution

as it raises the risk of toxicity and morbidity. NSAIDs, especially non-selective, cause prostaglandin inhibition, which directly affects renal function. This inhibition can result in mild to moderate problems that can progress to chronic kidney disease. As a result, the indication for this class of medications should be carefully considered, always confirming the risk-benefit ratio in addition to taking the patient's condition and any possible side effects into account. Patients should receive regular renal function monitoring and education of the possible dangers of NSAID use to their kidneys. It is advisable to counsel them to report kidney injury symptoms as soon as possible.

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