

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and Acute Kidney Injury (AKI)

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed in primary care for their analgesic and anti-inflammatory effects. However, NSAIDs and also selective COX-2 inhibitor are known as drug-induced acute kidney injury (AKI) that is frequently encountered by clinicians. These drugs reduce afferent arteriolar blood flow by antagonizing vasodilatory prostaglandins in patients with true or effective intravascular volume depletion or underlying chronic kidney disease (CKD). In this situation, glomerular filtration rate (GFR) drops and AKI develops, which is often rapidly reversible but sometimes associated with ischemic tubular injury. A second form of hemodynamic AKI may be caused by using NSAIDs in CKD patients which were treated with angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) which decreases GFR by lowering arterial blood pressure and dilating the efferent arteriole. These medications should be prescribed for the shortest duration, the lowest effective dose, and with careful surveillance to monitor nephrotoxicity precisely. NSAIDs should be used with special caution in elderly patients.

Keywords: NSAIDs; Acute Kidney Injury; Aspirin; COX-1; COX-2; Prostaglandin; Angiotensin Converting Enzyme Inhibitor; Angiotensin Receptor Blocker; Chronic Kidney Disease; Glomerular Filtration Rate

Abbreviations

NSAIDs: Non-steroidal Anti-inflammatory Drugs; AKI: Acute Kidney Injury; CKD: Chronic Kidney Disease; ACE-I: Angiotensin Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; GFR: Glomerular Filtration Rate; COX: Cyclooxygenase; PG: Prostaglandin; GI: Gastrointestinal; CHF: Congestive Heart Failure; SCr: Serum Creatinine; AIN: Acute Interstitial Nephritis; ADEs: Adverse Drug Events

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Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) represent one of the most common classes of medications used [1]. NSAIDs exert anti-inflammatory, analgesic and anti-pyretic effects through the suppression of prostaglandin (PG) synthesis, by inhibiting the enzyme cyclooxygenase (COX). Two isoforms of this enzyme COX-1 and COX-2 are known to exist [2]. Renal side effects vary with the extent of COX-2 and COX-1 selectivity and the administered dose of these compounds. While young healthy subjects will rarely experience adverse renal effects with the use of NSAIDs, elderly patients and those with co-morbidity who were treated with drug combinations may develop acute kidney injury (AKI). NSAIDs account for 21–25% of adverse drug events (ADEs) around the world. Moreover, they are also implicated in hospital admissions due to gastrointestinal, cardiovascular and renal ADEs [3,4].

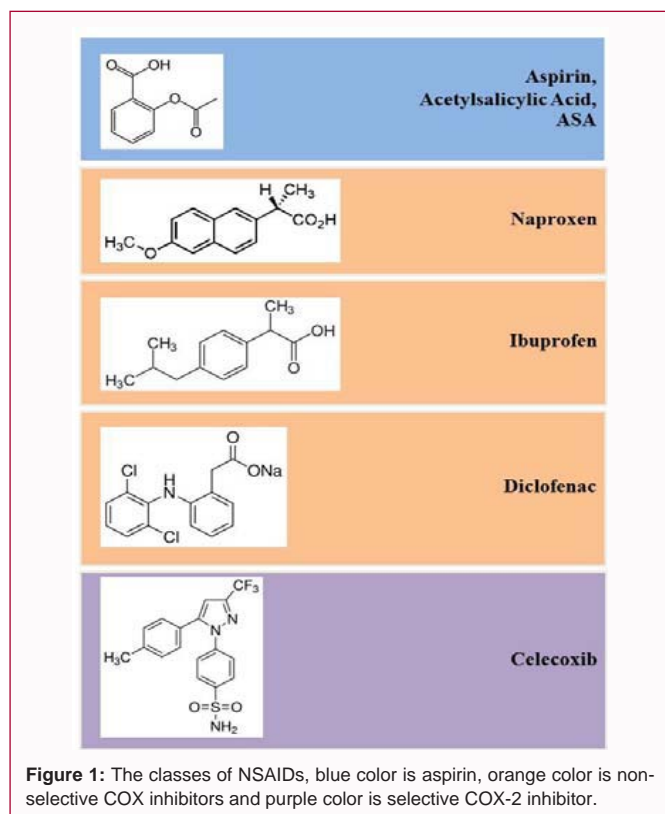
Classes of NSAIDs

Aspirin

Acts to irreversibly inhibit COX-1 and COX-2 by covalent acetylation of serine residues in their respective active sites. Low doses of aspirin can permanently suppress platelet COX-1 activity by 95% or more, since platelets lack of DNA and cannot synthesize new enzyme (Figure 1).

Non-selective COX inhibitors

Different non-selective NSAIDs have varying inhibitory effects against COX-1 and COX-2. The two most commonly used over-the-counter drugs (ibuprofen and naproxen) produce reversible platelet inhibition ranging from 50 to 95% in a reversible time-dependent manner that may be insufficient to provide cardio-protection. Ibuprofen and naproxen are also relatively non-selective



for inhibiting COX-1 and COX-2, and therefore can produce unwanted side effects by inhibiting both isoforms.

Coxibs

Selective COX-2 inhibitors were designed and marketed to avoid the gastrointestinal (GI) side effects known to result from suppression of protective prostaglandins synthesized by COX-1 in the GI mucosa. Their use led to the first reported incidence of increased cardiovascular events in 2004. Celecoxib has a 10-20 fold selectivity for COX-2 over COX-1 [6].

Pathophysiology of COX inhibition

PGs regulate a wide variety of renal functions, prostaglandin E₂ (PGE₂) is considered to be mainly a tubular PG and prostaglandin I₂ (PGI₂) is a vascular PG. PGE₂ which is located in nephrons, renal medullary interstitial cells and collecting tubules, is a vasodilator and plays a major role in excretion of salt and water by the kidney. PGE₂ regulates sodium and chloride transport in the loop of Henle and modulates water transport and renal medullary blood flow. PGE₂ are mediated through the four G-protein-coupled trans-membrane prostaglandin receptors prostaglandin E₂ receptor 1 (EP1), EP2, EP3 and EP4. PGI₂ regulates renal vascular tone, GFR and renin release [7,8]. In a person with normal renal hemodynamic parameters, PGs do not play a dominant physiologic role in maintaining renal blood flow and GFR. Selective COX-2 inhibitors were developed to reduce the GI side effects of NSAIDs. However, COX-2 appears to be associated with renal vascular tissues and podocytes and has been implicated as the dominant COX at the macula densa and in the medullary interstitium. The constitutive COX-2 in the human kidney and the profound effects of PGs on renal homeostasis may indicate that COX-2 inhibitors have the same potential renal side effects as traditional NSAIDs. Therefore, the same precautions in patients at risk for adverse renal effects probably apply to both the nonselective

NSAIDs and COX-2 selective inhibitors [9].

In normotensive subjects, nonselective NSAIDs or COX-2 inhibitors do not affect blood pressure and renal function. In contrast, inhibition of PG synthesis leads to renal decompensation in situations where renal and systemic hemodynamics is dependent on the availability of PGs. Moreover, in salt-depleted healthy subjects, elderly patients with impaired renal function or hypertension, NSAIDs may cause sodium and potassium retention, GFR reductions, induction of edema and elevations of blood pressure. Three groups of patients who are at risk for renal adverse effects from NSAIDs include extreme liver dysfunction (decompensated cirrhosis), chronic kidney disease (CKD) and congestive heart failure (CHF) due to reduction in renal blood flow and GFR [10].

Acute Kidney Injury (AKI)

Acute kidney injury (AKI) results in the abrupt loss of kidney function, leading to the retention of waste products, electrolyte disturbances, and volume status changes. The term AKI has replaced acute renal failure because smaller changes in kidney function without overt failure can result in significant clinical consequences and increased morbidity and mortality. The definition of AKI is an abrupt increase in serum creatinine (SCr) of 0.3 mg/dL over baseline within 48 hours, a 50% or greater increase in SCr within 7 days, or urinary output of less than 0.5 mL/kg/hour for more than 6 hours [11] (Table 1).

NSAIDs and AKI

It is estimated that 1-5% of NSAIDs users may develop renal adverse effects, both AKI and CKD. Various forms of AKI caused by NSAIDs have been observed including AKI, renal papillary necrosis, acute interstitial nephritis, hyperkalemia and volume retention [12]. Acute form of these side effects are dose/duration-dependent and usually reversible. Selective and nonselective NSAIDs should be avoided in patients with CKD, CHF, or decompensated liver cirrhosis to prevent nephrotoxicity. Some medications, such as Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II-receptor blockers and β -blockers, may also increase NSAIDs-related nephrotoxicity [13].

The pathophysiology of this phenomenon is reduction in afferent blood flow or pressure due to hypotension, volume loss; decreased cardiac output or renal artery stenosis can lower the intra-glomerular pressure and result in impaired renal function. In this situation, prostaglandin synthesis is increased and plays an increasingly important role in maintaining renal perfusion by causing enhanced pre-glomerular vasodilation [14] [Figure 2 (A)]. Under these conditions, NSAIDs and COX-2 inhibitors can adversely affect renal function by blocking the production of auto-regulatory prostaglandins, resulting in a decline in GFR that can ultimately result in acute kidney injury [Figure 2 (B)]. Moreover, in hypertensive patients with impaired renal function who were treated by using ACE-inhibitors or ARB can also further reduce glomerular perfusion and contribute to renal failure [15] (Table 1).

French Pharmacovigilance database showed serious adverse drug reactions (mostly AKI) in 24.2% of the patients on the combination therapy with NSAIDs and antihypertensive drugs, suggesting drug-drug interaction [16]. Moreover, a nested case-control study demonstrated that NSAIDs and renin-angiotensin system inhibitors and/or diuretics used in combination result in a higher incidence of

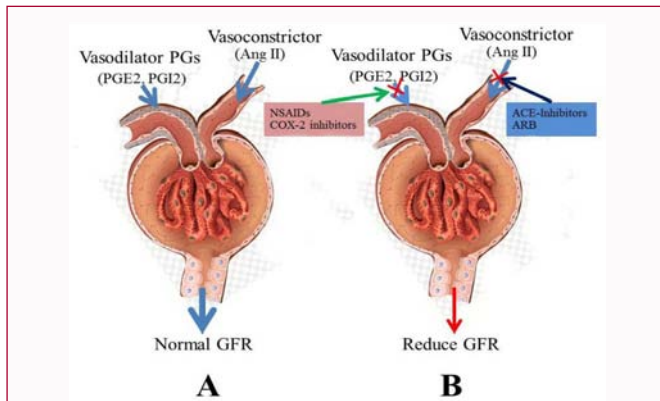


Figure 2: Regulation of renal blood flow & glomerular filtration in the kidney. PGE2 and PGI2 play an increasingly important role in maintaining renal perfusion by causing enhanced pre-glomerular vasodilation and angiotensin II (Ang II) produce efferent arteriole vasoconstriction to maintain normal GFR (A). Treatment by NSAIDs and COX-2 inhibitors can adversely affect renal function by blocking the production of autoregulatory prostaglandins resulting in a decline in GFR and treatment with ACE inhibitors or ARBs can also further reduce glomerular perfusion and contribute to renal failure (B).

AKI than previously thought [17]. Schneider et al. also reported the study that included 121,722 patients older than 65 years of age, the highest risk for AKI was demonstrated within 30 days after initiating NSAIDs therapy and decline after that. The relative risk for AKI for nonselective NSAIDs (other than naproxen), naproxen, rofecoxib, and celecoxib was 2.3, 2.4, 2.3, and 1.5, respectively, compared to the untreated control subjects [18]. In 2015, Camin et al. showed that diuretics therapy was the main drug which enhances the effect of NSAIDs and ACE inhibitors or ARBs. They concluded that diuretics in monotherapy, dual and triple combination therapy (Triple Whammy) have an elevated incidence of AKI. Dual therapies including diuretics show the same incidence of AKI as the Triple Whammy [19]. The profile of the at-risk patient is an elderly patient with an underlying renal or cardiac disease. The problem does not seem to be the drug itself but the onset of a concurrent disease-causing hypovolemia. Monitoring renal function and potassium levels is recommended when these therapies are initiated. In cases of concurrent disease, the temporary discontinuation of the Triple Whammy drugs, particularly diuretics, is recommended. In 2016, Chou et al. reported that the use

of nonselective NSAIDs rather than COX-2-selective NSAIDs was associated with increased risk of hospitalization for AKI within 1 month of 1st prescription (0.3-1.8% in cases vs. 0.1-1.1% in controls for COX-2 selective NSAIDs, $p > 0.05$ compared with 7.1-9.7% in cases vs. 1.4-2.4% in controls for non-selective NSAIDs, $p < 0.001$). They concluded that In a large “real-world” Asian population, the use of non-selective NSAIDs rather than COX-2 inhibitors is associated with an increased risk of AKI requiring hospitalization, especially within 1 month after prescription [20].

NSAIDs and Acute Interstitial Nephritis

Acute interstitial nephritis (AIN) is a renal lesion characterized by a rapid deterioration in kidney function with inflammation and edema of the renal interstitium [21]. NSAIDs and coxibs may produce AIN and can progress in some cases to CKD. AIN is caused by an immunological reaction after NSAID exposure of about a week. Drug-induced AIN is not dose-dependent and accounts for about 15 - 20% of all patients with AKI. It has been estimated that 2.7% of AKI is due to NSAID induced AIN among children [22]. Early diagnosis and quick discontinuation of the medication usually results in full recovery.

Presentation and Diagnosis of AKI

There are no specific signs or symptoms for NSAIDs induced acute kidney injury. Symptoms of acute kidney injury can be non-specific and may include shortness of breath, fatigue, confusion, nausea, and decreased urine output and ankle/leg swelling. Patients with pre-renal injury may have signs of volume depletion (eg, tachycardia, absolute or postural hypotension, low jugular venous pressure, dry mucous membranes). Patients with interstitial nephritis may have features of a systemic hypersensitivity including fever, arthralgia and a pruritic erythematous rash. Eosinophilia may also be present.

NSAIDs and Chronic Kidney Disease (CKD)

Stürmer et al. evaluated whether the half-life of NSAIDs may interfere with kidney function or not. They demonstrated that NSAIDs with intermediate-long half-life may affect a greater risk of CKD due to their sustained inhibition of PGs leading to a prolonged reduction in renal blood flow [23]. Recently, a nested case-control study showed a discrepancy among NSAIDs regarding the risk of chronic kidney

Table 1: Acute kidney injury network (AKIN) criteria for AKI definition.

| Stage | Increase in SCr | Urinary Output Change |
|-------|---|---|
| 1 | 1.5- to 1.9-fold ↑ SCr or ↑ SCr ≥ 0.3 mg/dL | < 0.5mL/kg/hr for 6–12 hr |
| 2 | 2- to 2.9-fold ↑ SCr | < 0.5mL/kg/hr for ≥ 12 hr |
| 3 | 3-fold SCr or SCr > 4 mg/dL with acute risk > 0.5mg/dL or RRT | < 0.3mL/kg/hr for ≥ 24hr or anuria for ≥ 12hr |

AKI: Acute Kidney Injury; RRT: Renal Replacement Therapy; SCr: Serum Creatinine.

Table 2: Risk factors for NSAIDs induced AKI.

| Risk Factors | Effects |
|--|---|
| -Increasing age -Hypertension -Atherosclerosis | -Renal afferent arterioles narrowing (reduce the capacity of dilation by PGs) |
| -Renal insufficiency | -Renal afferent arteriole is likely to be required to maintain GFR |
| -Volume depletion <ul style="list-style-type: none"> • True volume depletion (GI or renal salt and water losses, blood loss, diuretic use) • Effective volume depletion (liver cirrhosis or heart failure) | -Lowers afferent arteriolar pressure and stimulates secretion of angiotensin II |
| -Use of ACE inhibitors or ARBs | - ACE inhibitors and ARBs prevent efferent arteriole vasoconstriction which is very important in maintenance of GFR |
| -Use of the “Triple whammy” (ACE inhibitor or ARB plus diuretic plus NSAID) | -Diuretic may cause volume depletion |

damage. Long-term use of oxicams, NSAIDs with long half-life, is associated with an increased risk of CKD. Likewise, short-term use of ketorolac is also associated with an increased risk of CKD. This occurs most likely in patients with subclinical CKD in whom a decline in renal function have been triggered by ketorolac [24]. Nderitu et al. found that high-dose, but not regular-dose NSAID significantly increase the risk of accelerated CKD progression and suggested that stopping of NSAIDs in the medium term is needed in patients with moderate to severe CKD. NSAIDs are recommended to be used at the lowest effective dose [25]. In conclusion, regular-dose NSAID use did not significantly increase the risk of CKD progression. Chronic use of NSAIDs in some patients, particularly those with other risk factors may result in end-stage chronic renal disease. The risk of CKD varies across individual NSAIDs. In patients with CKD, NSAIDs should be prescribed at the lowest effective dose.

Treatment

Renal function will recover in most patients after withdrawal of NSAIDs therapy. Steroids may aid recovery in patients with interstitial nephritis who does not improve after stopping NSAIDs therapy. NSAIDs use should be avoided in the future in such patients.

Prevention of NSAIDs Related AKI

Because of the frequency of NSAIDs use and the significant risk of adverse effects, it is important to be aware of their proper use. NSAIDs prescribing guidelines minimize the risk of NSAIDs-induced toxicity, as well as unnecessary health care expenditure [26]. NSAIDs should only be used precisely as indicated by a physician, at the lowest effective dose, and for the shortest possible time excepted in very specific cases, continued long-term use may be justified. Physician should consider other treatment options before prescribing NSAIDs. The use of two or more of NSAIDs is known to be associated with a higher, cumulative risk of adverse effects. NSAIDs should be used with caution in elderly people and topical NSAIDs are recommended as a preferred treatment before oral NSAIDs for patients at age ≥ 75 years. Monitoring of renal function should be considered after beginning NSAIDs treatment in patients at risk of renal failure [27].

Conclusion

Treatment by using NSAIDs with therapeutic doses and for shorter duration, the majority of the patients usually tolerate them well. However, with higher doses and longer duration of treatment and in the presence of comorbidities, the risk of adverse effects is increased. The renal adverse effects of NSAIDs may be prevented by performing careful assessment of the patient's risk factors and by limiting the dose and duration of treatment with NSAIDs. In patients at risk physician should closely monitoring renal function and blood pressure abnormalities.

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