

MANIFESTATIONS OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS-INDUCED KIDNEY DISORDERS

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly prescribed medication.¹ The gastrointestinal tract and kidneys are important targets of clinical events associated with the use of NSAIDs.² Selective COX-2 inhibitors have minimal gastrointestinal side effects. However, the newer NSAIDs also has nephrotoxic effects remain as nonselective NSAIDs.¹

The kidneys are the major organ for drug excretion, so that the renal arterioles and glomerular capillaries are especially vulnerable to the effects of drugs.³ The spectrum of NSAID-induced nephrotoxicity includes acute tubular necrosis, acute tubulointerstitial nephritis, glomerulonephritis, renal papillary necrosis, chronic renal failure, salt and water retention, hypertension, and hyperkalemia.¹

Among the various clinical complications, the effects on the kidney are probably the most common and severe due to the use of NSAIDs.⁴ Fifty million US citizens report NSAIDs use, and it has been estimated that 500.000 – 2,5 million people will develop NSAID nephrotoxicity in the US annually.⁵ It has been reported that 37% of drug-associated acute renal failure is associated with the use of NSAIDs, and NSAID-induced acute renal failure accounts for 7% of overall cases of acute renal failure.⁴

This review discusses the NSAIDs, mechanisms and clinical manifestations of NSAID-induced renal impairment and some NSAID options that can be used in patients with renal failure.

NSAIDs

NSAIDs have their origin in the extracts of salicylate-containing plants, in particular were

known for their antipyretic, analgesic and anti-inflammatory properties.⁶ NSAIDs exerts anti-inflammatory, analgesic and anti-pyretic effects through the suppression of prostaglandin (PG), by inhibiting the enzyme cyclooxygenase (COX). Two isoforms of this enzyme COX-1 and COX-2 are known to exist. Nonselective NSAIDs inhibit both COX-1 and COX-2.² Selective NSAIDs (*COX-2 selective inhibitors*) inhibiting only the COX-2 isoform.⁷

Pharmacokinetics of NSAIDs

Most NSAIDs are organic acids and are well absorbed in the gastrointestinal tract without substantial decreases in their bioavailability with the highest concentration 1 to 4 hours. NSAIDs undergoes metabolism in the liver and are excreted through the kidneys. NSAIDs is largely bound to albumin in the blood (95% -99%) and have low volume of distribution. NSAIDs may cross the blood brain barrier depending on lipid solubility. The half-life varies for different NSAIDs, but are generally divided into short (<6 hours) and long (>6 hours). Mechanisms of action and side effects of NSAIDs for each patient varies depending on the type of NSAID used. This difference arises because of differences in the absorption, distribution and metabolism in the human body.⁸

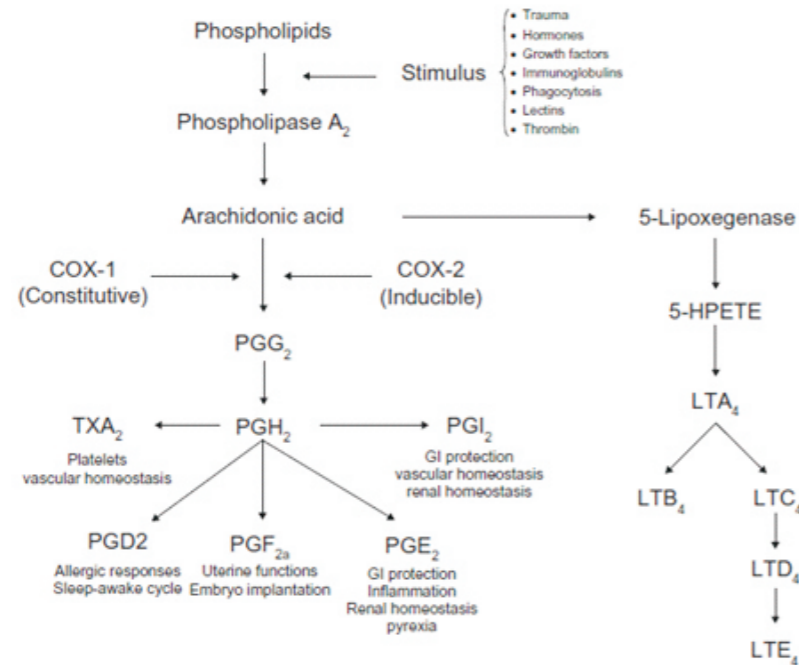
Physiological Role of Prostaglandins in the Kidney

Prostaglandins were first described by Goldblatt as substances produced by the prostate gland and contained in the seminal fluid, with antihypertensive properties. Subsequently, it was shown that prostaglandins are produced by a large variety of cells in the human body. During the

biosynthesis of prostaglandins, cyclooxygenase (COX or *prostaglandin H synthase*) catalyses the conversion of arachidonic acid to prostaglandin endoperoxidases, prostaglandin G₂ (PGG₂) and then PGH₂. PGH₂ is the precursor of the biologically

active prostaglandins and thromboxanes. PGH₂ is then isomerized into various prostanoids such as thromboxane A₂ (TXA₂), prostacyclin (PGI₂), PGD₂, PGE₂ and PGF_{2α}.⁶

Figure 1. The arachidonic acid cascade⁶



Prostaglandins regulate a wide variety of renal functions. Prostaglandins maintain renal blood flow and glomerular filtration rate (GFR), especially in fluid depleted states. PGE₂ is considered to be mainly a tubular PG and PGI₂ a vascular PG. However, renal arterioles, tubules, medullary interstitial cells and mesangial cells are able to produce both PGE₂ and PGI₂. The physiological effects of PG₂ are mediated through the four G-protein-coupled transmembrane prostaglandin receptors EP₁, EP₂, EP₃, EP₄.² Locally synthesized prostaglandins PGI₂ (prostacyclin), PGE₂ and PGD₂ cause vascular dilatation, diminish vascular resistance and enhance renal perfusion with redistribution of blood flow from the renal cortex to nephrons in the juxta-medullary region. PGE₂ and PGF_{2α} cause diuresis and natriuresis by inhibiting the transport of sodium and chloride in the thick ascending limb of loop of Henle and the collecting

ducts. PGE1 tends to counteract the action of antidiuretic hormone (vasopressin).¹

In volume contracted states, renin-angiotensin-aldosterone axis are stimulated with increased renin, angiotensin II, and aldosterone production resulting in renal vasoconstriction and increased sodium and chloride reabsorption. There is increased sympathetic outflow, which further increases the vascular tone. In that setting, prostaglandins provide compensatory vasodilation of renal vascular bed and ensure adequate renal blood supply. PGE₂, PGD₂ and prostacyclin cause vasodilation by depressing norepinephrine release. PGE₂ antagonizes the vasoconstrictive action of angiotensin II on afferent arterioles.^{1,7}

NSAID-induced renal impairment can be grouped according to their effects on prostaglandin PGE₂ and PGI₂. When the production of PGI₂ is blocked, hyperkalemia and acute renal failure can

result. The effect of blocking the production of PGE₂ may include peripheral edema, increased blood pressure, weight gain and through rare, congestive heart failure.⁷

There are two kinds of COX enzymes, COX-1 and COX-2. Both of these proteins have the same molecular weight, but are structurally distinct in their substrate binding sites, which are smaller in COX-1 than in COX-2. The active site of COX lies in a narrow hydrophilic tunnel composed of an active inner site and protected by an outer area that is made up of three α helices. NSAIDs attaches to these outer helices and temporarily prevent the passage of arachidonic acid from reaching the active site and triggering the production of prostaglandins.⁶

COX-1 is constitutively expressed in most cells and is involved in physiological processes. The COX-1 expression is also found in fetal and amniotic cells, uterine epithelium in early pregnancy and in the central nervous system. COX-2 was considered to be induced by inflammation and the presence of proinflammatory cytokines and mitogens.⁶ In general, COX-1 functions in the control of renal hemodynamics and glomerular filtration rate; COX-2 functions affect salt and water excretion, although there is some overlap. This

separation of COX-mediated functions in the kidney is based in part on the physiologic / anatomic distribution of COX-1 compared to COX-2.⁷ Blockade of either or both of these enzymes can have different effects on renal function.²

Risk Factors of NSAID-induced Renal Side Effects

There is an increased risk of developing renal damage in patients who regularly consume NSAIDs. This risk increases with advanced age and other comorbidities. Age-related changes in renal function predispose to nephrotoxicity, especially when there is a decrease GFR, decreased renal blood flow and increased renal vascular resistance, dehydration or impaired liver function. The risk of renal dysfunction is further enhanced by the presence of sepsis, multiple organ dysfunction, and critical illness in general. Recent analysis of general practice database in the United Kingdom, current users of NSAIDs had a relative risk of acute renal failure of 3.2 (95% confidence interval, 1.8-5.8). This risk increased with comorbid illness and in particular it increased dramatically to 11.6 (95% confidence interval, 4.2-32.2) when concomitant diuretics were being taken.⁴

Table 1. Risk Factors for NSAID-induced Renal Side Effects in the Elderly Population⁴

Risk Factors for NSAID-Induced Renal Side Effects in the Elderly Population
Age-related changes in renal function
Decreased renal functional reserve
Decreased glomerular filtration rate
Decreased total renal blood flow
Increased renal vascular resistance
Diabetes mellitus
Altered pharmacokinetics
Increased free drug concentration
Dehydration
Reduced drug distribution volume
Hypoalbuminemia
Decreased elimination of the drug via alternative pathways
Interaction with other drugs
Diuretics
ACE inhibitors
Beta blockers

Mechanisms of Drug-induced Acute Kidney Injury

There are several mechanisms of *drug-induced acute kidney injury* include vasoconstriction, altered intraglomerular hemodynamics, tubular cell toxicity, interstitial nephritis, crystal deposition, *drug-induced thrombotic microangiopathy*, osmotic nephrosis, and rhabdomyolysis. The mechanisms associated with NSAIDs use was altered intraglomerular hemodynamic and interstitial nephritis.

1. Altered Intraglomerular Hemodynamics

Altered intraglomerular hemodynamics are responsible for the decline in renal function seen with NSAIDs, angiotensin converting enzyme inhibitors (ACEI), *angiotensin receptor blockers* (ARB). In patients with hemodynamic instability and volume depletion, renal perfusion becomes prostaglandin-dependent. Renal dysfunction that accompanies antihypertensive therapy is a result of excessive lowering of blood pressure. ACEI and ARB are more commonly associated with this complication because any decline in intraglomerular pressure due to blood pressure lowering will be exaggerated by concomitant vasodilation of the efferent arteriole. And even without a decline in blood pressure, the decrease of efferent resistance may result in a lower GFR in patients where constriction of the efferent arteriole serves to minimize the decline in GFR such as in patients with absolute or effective reduction in intravascular volume, in patients with obstructive renal vascular disease or in patients receiving drugs associated with afferent vasoconstriction.⁹

2. Interstitial Nephritis

Acute interstitial nephritis defines a pattern of renal injury usually associated with an abrupt deterioration in renal function characterized histopathologically by inflammation and edema of the renal interstitium.¹⁰ It occurs on the allergic basis in an idiosyncratic and nondose-dependent manner.⁹ The nature of this disorder is usually diagnosed through a kidney biopsy.⁴ Acute interstitial nephritis has become an important cause of acute renal failure due to the increasing use of antibiotics and other medications such as NSAIDs that may induce an allergic response in the interstitium.¹⁰ Interstitial nephritis can occur in association with NSAIDs due

to allergic reaction, direct cellular toxicity, alteration of metabolic pathways and possibly obstruction. These complex and multifactorial mechanisms may also combine with hemodynamic perturbations. In some cases, the damage becomes extensive, leading to papillary necrosis.⁴

The onset after drug exposure ranges from 3 to 5 days with a second exposure up to several weeks with the first exposure.⁹ Acute interstitial nephritis symptoms develop within 3 weeks after the inciting drug in about 80% of patients. The typical presentation is a sudden impairment in renal function, mild proteinuria (<1g/day), abnormal urinalysis, flank pain, normal blood pressure and no edema. Hematuria and pyuria are present in approximately one-half of patients, with leukocyte casts. Occasionally, patients have a low fractional excretion of sodium.¹¹

Manifestations of NSAID-induced Kidney Disorders

1. Sodium Retention, Edema, and Hypertension

The use of non-selective NSAIDs or selective NSAIDs may be complicated by the development of significant sodium retention, edema, congestive heart failure, and hypertension. COX-2 inhibition likely promotes salt retention via multiple mechanisms. Reduce GFR may limit the filtered sodium load and salt excretion. In addition, PGE₂ directly inhibits sodium absorption in the thick ascending limb and collecting duct. COX-2 inhibitors decrease renal PGE₂ production and thereby may enhance renal sodium retention. Finally, reduction in renal medullary blood flow by inhibition of vasodilators prostanoid may significantly reduce renal salt excretion and promote the development of edema and hypertension.¹²

2. Hyperkalemia

Non-selective NSAIDs cause hyperkalemia due to suppression of the renin / aldosterone axis. Both decreased GFR and inhibition of renal renin release may compromise renal potassium excretion. The study in patients with dietary salt restriction demonstrated that COX-2 selective inhibitor (either rofecoxib or celecoxib)

decreased urinary potassium excretion.¹² Patients with diabetes mellitus, CKD or both, hyperkalemia may develop after administration of NSAIDs. Other aggravating factors are simultaneous consumption of potassium-sparing diuretics, ACEI or ARB, and beta blockers. In these circumstances, hyperkalemia may be accompanied by a mild metabolic acidosis and a deterioration in renal function.⁴

3. Papillary Necrosis

Both acute and sub acute forms of papillary necrosis has been observed with NSAIDs use. Acute renal papillary injury associated with NSAID occurs more likely in the setting of dehydration. Long-term use of NSAIDs has been associated with papillary necrosis and progressive renal structural and functional deterioration much like the syndrome of analgesic nephropathy. Observational studies indicate that renal medullary interstitial cells are the early target of injury in analgesic nephropathy.¹²

Analgesic nephropathy is a slowly progressive chronic kidney disease resulting from daily use for many years of preparations containing at least two analgesics (e.g., Aspirin, acetaminophen) in combination with central-acting dependence-inducing substances, such as caffeine, codeine, and / or barbiturates. Analgesic nephropathy is characterized by capillary sclerosis, renal cortical atrophy, chronic interstitial nephritis and / or papillary sclerosis / necrosis / calcifications. In some patients with analgesic nephropathy, the uroepithelia can develop transitional cell carcinoma. Analgesic nephropathy can be accurately diagnosed or excluded by CT-scan without contrast media.²

4. Acute Renal Failure

NSAIDs may cause acute renal failure due to acute interstitial nephritis as a result of allergic hypersensitivity reaction few days after the initiation of NSAID therapy. In this case, kidney function usually recovers when NSAIDs are discontinued. Long-term NSAIDs use may result in chronic interstitial nephritis with interstitial fibrosis and chronic renal dysfunction.²

Acute renal failure is generally considered to be a result of altered intrarenal microcirculation and glomerular filtration secondary to the inability to produce beneficial endogenous prostanoids when the kidneys are dependent on them for normal function. Recent reports suggest that like the traditional, non-selective NSAIDs, COX-2 selective NSAIDs will also reduce glomerular filtration.¹²

There is some evidence to support an increased incidence of adverse effects with increased doses of selective and non-selective NSAIDs. Some medications, such as ACEI, ARB and beta blockers may increase NSAID-related renal complications. The high acute dose of NSAIDs has been implicated as causes of acute renal failure, particularly in the elderly. Some reported cases of acute renal failure after initiation of NSAIDs therapy include apparent in healthy subjects. Case reports have documented acute renal failure in association with both celecoxib and rofecoxib. Of 1799 *frail* elderly patients hospitalized with community-acquired acute renal failure, 18.1% were current users of prescribed NSAIDs. In this study, a strong dose-dependent increase of risk for acute renal failure was observed in 35% subjects taking ibuprofen.²

Table 2. Predisposing factors for NSAID-Induced Acute Renal Failure¹³

Predisposing Factors for NSAID-Induced Acute Renal Failure
Decreased effective blood volume (eg, from congestive heart failure, cirrhosis, nephrotic syndrome, anesthesia, shock)
Decreased absolute volume (eg, from hemorrhage, sodium and water depletion)
Acute renal failure
Chronic kidney disease
Medications (eg, angiotensin -converting enzyme inhibitor, angiotensin receptor blocker, aldosterone receptor antagonist, diuretics, cyclosporine)
Renal transplantation
Advanced age

5. Nephrotic Syndrome

Nephrotic syndrome typically occurs in patients who are chronically taking NSAIDs within a period of several months. The renal pathology is usually consistent with *minimal change disease* with foot process fusion of glomerular podocytes, but membranous nephropathy has also been reported. Typically, nephrotic syndrome occurs together with interstitial nephritis. Nephrotic syndrome without interstitial nephritis may occur, as well as immune-complex glomerulopathy, in a small subset of patients receiving NSAIDs. It remains uncertain whether this syndrome results from mechanism-based cyclooxygenase inhibition by these drugs, an idiosyncratic immune drug reaction or a combination of both.¹²

6. Renal Dysgenesis

Reports of renal dysgenesis and oligohydramnions in offspring of women administered non-selective NSAIDs during the third trimester of pregnancy have implicated prostaglandins in the process of normal renal development. A similar syndrome of renal dysgenesis has been reported in mice with targeted disruption of the COX-2 gene, as well as mice treated with the specific COX-2 inhibitor. A report of renal dysgenesis in the infant of a woman exposed to the COX-2 selective inhibitor nimesulide suggests COX-2 also play a role in renal development in humans.¹²

The intrarenal expression of COX-2 in the developing kidney peaks in mouse at post-natal day 4 and in the rat in the second post-natal week. It has not yet been determined if a similar pattern of COX-2 is seen in humans.¹² COX-2 is expressed continuously not only in the adults but also in the fetal kidney. COX-2 dependent PG formation is necessary for normal renal development. Prostanoids or other products resulting from COX-2 activity in the macula densa may act in a paracrine manner to influence glomerular development. Mice deficient COX-2 exhibit renal dysgenesis. In contrast, research on gene showed that COX-1 disruption does not interfere with normal renal development. Administration of a COX-2 selective inhibitors during pregnancy significantly impaired development of renal cortex and reduced glomerular diameter in mice, while administration of a COX-1 selective inhibitor did not affect renal development.²

7. Worsening of Chronic Kidney Disease (Acute on Chronic Renal Failure)

The use of NSAIDs is often associated with worsening of mild to moderate *chronic kidney disease* (CKD), with a significant reduction of GFR and the evolution of CKD toward more advanced stages. Direct toxicity to the tubules is manifested by loss of polarity, loss of *tight junctions*, loss of cell substrate adhesion, exfoliation of viable cells from the tubular basement membrane and aberrant renal

cell-cell adhesion. Further damage may contribute to altered gene expression, cellular differentiation and lethal injury such as necrosis or apoptosis. Tubular necrosis is characterized by severe depletion of cellular stores of adenosine triphosphate, reduced activity of membrane transport pumps, cell swelling, increase in intracellular free calcium, activation of phospholipases and proteases, depletion of glycine and plasma and subcellular membrane injury.⁴

Patients at risk for acute kidney injury by advanced age or dehydration, may experience abrupt worsening of CKD with reduction of glomerular filtration and *acute-on-chronic renal failure*. Additional risk factors include congestive heart failure, alcohol abuse, and chronic use of diuretics.⁴

Research on the relationship of regular use analgesics such as acetaminophen, aspirin, or NSAIDs with chronic renal dysfunction showed different results. A *case-control* study reported on 2-fold increased risk of *end-stage renal disease* among individuals with lifetime use of more than 1000 acetaminophen tablets and 8-fold increased risk among those with a lifetime cumulative dose of more than 5000 tablets NSAIDs. In contrast, multivariable analysis performed in a total 11,032 healthy men demonstrated that the relative risk of elevated creatinine levels associated with intake of in 2500 tablets or more analgesics were 0.83 for acetaminophen, 0.98 for aspirin, and 1.07 for other NSAIDs. There was no association observed between analgesic use and reduced creatinine clearance. A *case-control* study found a greater than 2-fold increased risk of newly diagnosed chronic renal insufficiency for regular users of acetaminophen or aspirin. In the *Nurse's Health* study, acetaminophen use was associated with an increased risk of GFR decline in 11 years, but not on the use of aspirin and NSAIDs. In contrast, any *case-control* studies found an association between NSAIDs and the risk of chronic renal dysfunction.²

Gooch *et al*, determined the association between NSAID use and progression of CKD in an elderly community-based cohort. A total of 10,184 subjects (average age 76 years) were followed for a median 2.75 years. High-dose NSAIDs users were associated with an increased risk for rapid CKD

progression among subjects with a *baseline* mean GFR between 60 and 89 ml/min/1.73 m² without risk differential between selective and non-selective NSAIDs users.² Many epidemiological studies have linked NSAIDs use and progression of CKD, but the risks of NSAIDs in patients with CKD so far supported only by consensus and theoretical effect, remain less clearly established by the evidence.¹⁴

Analgesic Therapy in Patients with CKD

Although primary care and general medicine textbooks and clinical practice guidelines recommend avoidance of NSAIDs for most CKD patients, clinicians should consider the risks and benefits on a case-by-case basis, with determination and consideration of their patients' CKD status and the use of NSAIDs.¹⁴

NSAIDs should be avoided or given cautiously in patients with stage 4 or higher CKD (GFR < 30ml/min). Pain management with NSAIDs in patients with CKD should be based on precise indications and given the limited time. NSAIDs should be initiated at the lowest effective dose and adjusted for those drugs that are excreted mainly by the kidneys as well as strict monitoring of blood pressure, body weight (as a marker of edema formation), renal function and electrolytes.¹³

1. Non-selective NSAIDs

NSAIDs are used as primary or *adjuvant* therapy at all steps of the WHO analgesic ladder. There is no evidence that they are more effective for certain types of pain rather than others. A meta-analysis of non-selective NSAIDs found no evidence for the analgesic superiority of one NSAID over others, but the side effect profiles can differ significantly.¹³

2. Aspirin and NSAIDs

In therapeutic doses, aspirin does not impair renal function in patients with normal renal function. But as well as other types of NSAIDs, patients with CKD may have a transient decrement in renal function with aspirin dosages above 325 mg / day. Aspirin and NSAIDs should not be merged because they may reduce GFR. NSAIDs may be deleterious to the cardioprotective effects of aspirin. Regular aspirin use does not influence hypertension or increase risk for CKD when given in

recommended doses for the prevention of cardiovascular events. Aspirin should be avoided in patients with acute glomerulonephritis, cirrhosis with ascites, and children with congestive heart failure to avoid potential nephrotoxicity. In all other conditions are accompanied with CKD, risk versus benefit should be assessed. If aspirin therapy should be given routinely, careful monitoring of renal function should be performed at regular interval.¹³

3. Selective COX-2 Inhibitors

CKD patients are at higher risk for adverse gastrointestinal events and bleeding. This group of drugs appears to be engaged in the CKD population. Unfortunately, patients with CKD were specifically excluded from many trials comparing selective COX-2 inhibitor with non-selective NSAIDs, and as a result, the gastrointestinal protective effects of COX-2 inhibitors have not been demonstrated in patients with advanced CKD.¹³

Selective COX-2 inhibitors appear to have a similar risk of reducing GFR and promoting adverse renal effects as compared with non-selective NSAIDs. Selective COX-2 inhibitor may be more potent inducers of hypertension than non-selective NSAIDs. Other adverse renal effects such as edema formation, hyponatremia, hyperkalemia, and metabolic acidosis are similar for selective COX-2 inhibitors and non-selective NSAIDs. Therefore, this drug should be prescribed with the same attention as all kinds of other NSAIDs.¹³

On a *case-control* study in Canada to assess the association between NSAIDs exposure, including COX-2 inhibitors and the hospitalization for acute renal failure, acute renal failure is comparable to rofecoxib, naproxen, and non-naproxen NSAIDs, but was borderline lower for celecoxib.¹⁵

4. Acetaminophen

The National Kidney Foundation recommends acetaminophen as the non-narcotic analgesic option for patients with CKD. Acetaminophen has potent analgesic and

antipyretic effects, but mild anti-inflammatory properties. Acetaminophen is a weak inhibitor of both COX-1 and COX-2 although the true mechanism of analgesia remains unknown. Acetaminophen is metabolized by the liver and does not require dose adjustment when used in CKD patients. There is no evidence that occasional use causes renal injury, but it has been suggested that very large doses for extended periods can cause papillary necrosis. When recommending acetaminophen to CKD patients, it is important to note is that many preparations contain a combination of acetaminophen with aspirin, NSAIDs and other potentially harmful ingredients. If acetaminophen are ineffective for pain control, *nonacetylated salicylates* (e.g. salsalate) may be an option and can be recommended for CKD patients.¹³

On a case-control study in Sweden, the regular use of acetaminophen was associated with a gain of 2.5 in the risk of chronic renal failure, and the relative risk increased with increasing cumulative lifetime doses.¹⁶

5. Tramadol

Tramadol, a centrally acting non-narcotic agent, is a potential alternative analgesic to NSAIDs, COX-2 inhibitors and acetaminophen for CKD patients. Tramadol acts on opioid receptors, has similar therapeutic and side-effect profile such as opioids, but without the same abuse potential. This drug also inhibits the reuptake of monoamines (norepinephrine and serotonin) by the nerve cells, which is believed to reduce central nervous system pain sensing.¹³

Tramadol is metabolized in the liver and eliminated by the kidneys. The elimination half-life of 5 hours is unpredictably increased in patients with CKD and possibly up to two times longer. To avoid drug toxicity, it is reasonable to prescribe dosages that do not exceed 200 mg / day for CKD patients with a GFR less than 30 ml / min (CKD stage 4 and 5).¹³

Table 3. Pain Medication Guidelines for Patients with CKD¹³

Pain Medication Guidelines for Patients with CKD
Determine the type, origin, and intensity of pain
Determine level of kidney function by 24-hour urine or GFR estimate equations
Review medication list of potential drug-drug interactions
Attempt to take the least nephrotoxic medication; consider shorter -acting drugs with limited toxic metabolites and low interaction potential
Generally begin therapy with a lower drug dose; adjust dose and interval based on level or stage of CKD
Increase compliance by informing patients of expected efficacy and toxicity
Consider prophylaxis for known adverse effects
Monitor medication levels if appropriate
Reassess kidney function and requirement for pain medication on a regular basis

CONCLUSION

NSAIDs exert anti-inflammatory, analgesic and anti-pyretic effects through the suppression of prostaglandin (PG), by inhibiting the enzyme cyclooxygenase (COX). Blockade of either or both of these enzymes can have different effects on renal function. However, both non-selective NSAID or selective NSAID often cause toxicity and renal abnormalities. The increased risk of renal impairment occurs in patients who regularly consume NSAIDs, advanced age, dehydration, impaired liver function, sepsis, multiple organ dysfunction, and critical illness in general. The mechanisms associated with NSAIDs use was altered intraglomerular hemodynamic and interstitial nephritis. Manifestations NSAID-induced kidney disorders include sodium retention, edema, hypertension; hyperkalemia; papillary necrosis; acute renal failure; nephrotic syndrome; renal dysgenesis and worsening of CKD. NSAID use in patients with CKD should be appropriate indications, starting with the lowest effective dose and with close monitoring.

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