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Analgesic nephropathy

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs), which are easily accessible, inexpensive and have many therapeutic effects, are used frequently and in large quantities by every age group of patients. NSAIDs reversibly inhibit cyclooxygenase enzymes at various degrees and they have the same action and toxicity mechanism. These groups of drugs can cause damage in many organs when there used at high dose and for a long-time period. Analgesic nephropathy is one of the prominent side effects of NSAIDs which damage kidneys. The present review focused on renal toxic mechanisms induced by NSAIDs. The geriatric group which is the most vulnerable group to misusage of NSAIDs should be well informed and monitored by healthcare professionals to decrease the risk of adverse effects related to NSAIDs.

Keywords

Analgesic, analgesic nephropathy, cortical tubulointerstitial nephritis, non-steroidal anti-inflammatory drugs, renal papillary necrosis.

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INTRODUCTION

Analgesic nephropathy is a kind of chronic renal incompetency which is caused by long term usage of one or more analgesic for medication. The specific medication and the dose interval required have not been fully understood (De Broe 1998). Analgesic nephropathy can be considered as one of the causes of end-stage renal failure (De Broe 1998; Chang *et al.* 2008). These patients generally had been taken analgesics for months or years because of chronic pain like headaches or backaches (Gault and Wilson 1978). Its pathological signs; include atrophic kidneys, renal papillary calcification, and irregular renal contour.

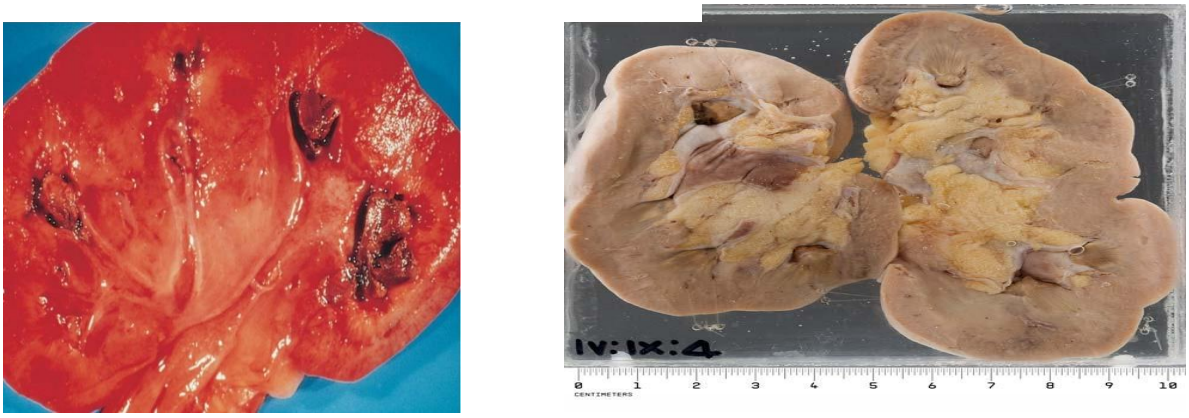

Figure 1: Pathological signs of analgesic nephropathy (Pinter *et al*. 2004; Noels *et al.* 1995; De Broe 2009).

A relation between non-steroidal anti-inflammatory agents (NSAIDs) and chronic kidney disease has long been under investigation. NSAIDs are the most commonly used medicines in the treatment of pains, inflammations and fever. NSAIDs are accessible, cheap, and can be sold with or without prescription (Buer 2014).

Chronic pain is a treatable condition that at any one point in time affects 20%–46% of community-dwelling older adults and 28%–73% of residents in aged-care facilities. A number of practice guidelines and literature reviews related with to the management of chronic pain in the elderly patients suggest paracetamol as the first-line management option (Abdulla *et al.* 2013). Several case-control studies have reported associations between chronic renal failure and other analgesic preparations, including aspirin, antipyretics, and NSAIDs in combination with caffeine, codeine, and/or barbiturates (De Broe 2009). It has been proposed that paracetamol, not phenacetin, accumulated in the renal papilla, and in animal experiments phenacetin appeared to be less nephrotoxic than the other analgesics (Bluemle 1969).

In the 1950s, researchers in Sweden and Switzerland illustrated that renal papillary necrosis developed from long term ingestion

of large number of phenacetins containing analgesic mixtures. During the 1960s and 1970s, phenacetin was singled out as the nephrotoxic agent in the analgesic mixtures, leading to its ban in several countries. Thereafter, the incidence has declined markedly. The nephrotoxicity of phenacetin is dose dependent. An intake of 6–8 tablets per day for a period of 6–8 years lead to the development of AN (Nanra *et al*. 1987).

Continuous and persistent consumption of NSAIDs cause many adverse effects in the body. Especially, prolonged use can cause damage to the kidneys and lead to the development of nephropathy. The major aim of present study was to review nephrotoxicity mechanisms induced by NSAIDs. For this purpose, many literatures were reviewed and under the light of these literatures the mechanisms of analgesic nephropathy were evaluated in detail.

Therapeutic effect mechanism of NSAIDs

NSAIDs reversibly inhibit cyclooxygenase (COX) enzymes at various degrees. Prostaglandins are responsible in functional regulation of several organs such as the gastrointestinal tract (maintaining GI mucosal integrity), increase renal blood flow, promote blood clotting by activating platelets, and also affect kidney function (Hawkey 2001). However, excessive number of prostaglandins are responsible for enhancing fever, inflammation and pain. Therefore, inhibiting prostaglandin production can cause adverse effects even in the therapeutic range of NSAIDs usage. There are two types of isoenzymes, COX-1 and COX-2, which were identified in early 1990s and known to be involved in production of prostaglandin. The main role of COX-1 is to produce prostaglandins and COX-2 become induced in response to inflammation (Hilário *et al.* 2006). Figure 2 shows the arachidonic acid pathway. The location of isomerases of the prostaglandins have be shown in Figure 3.

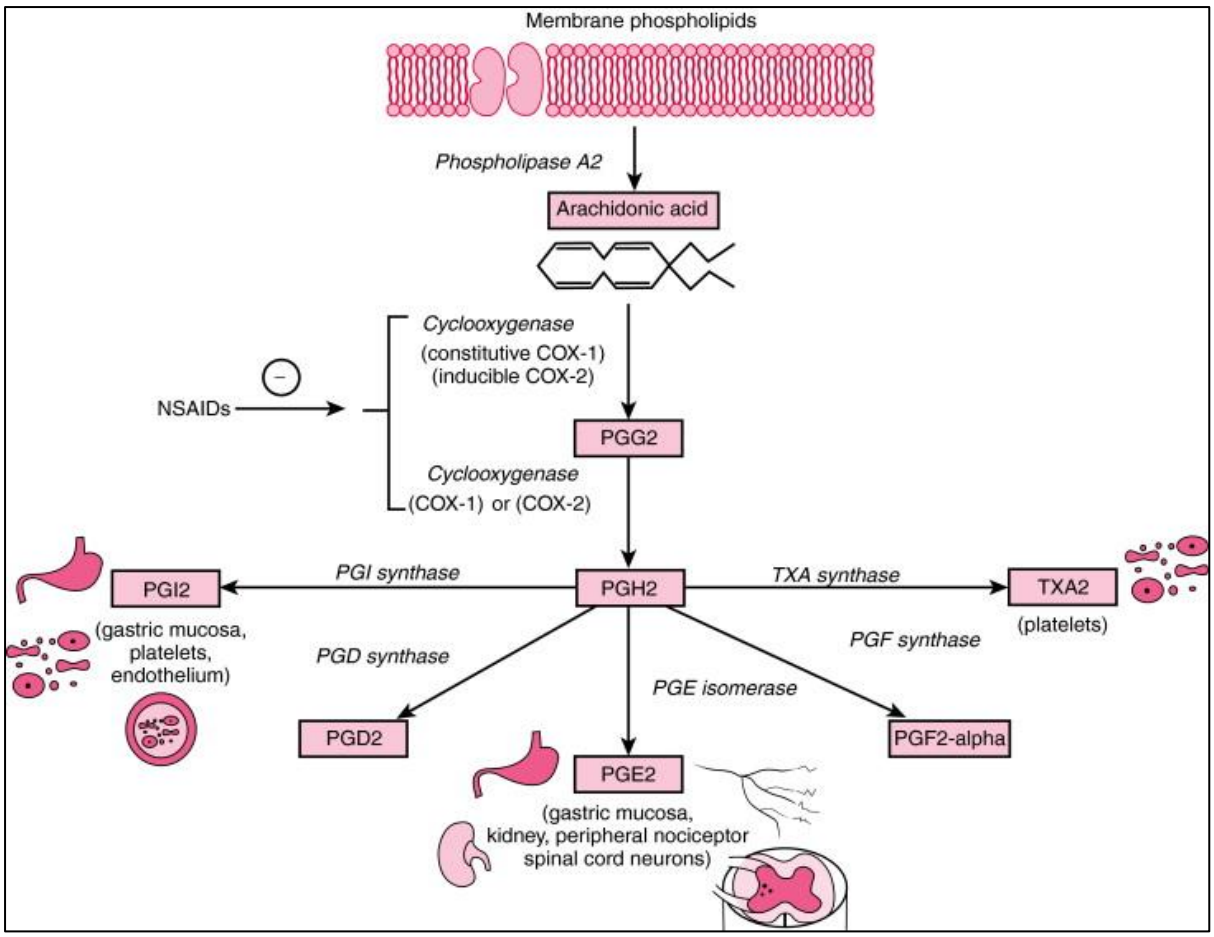

Figure 2: Arachidonic acid pathway (Kawahara *et al.* 2015)

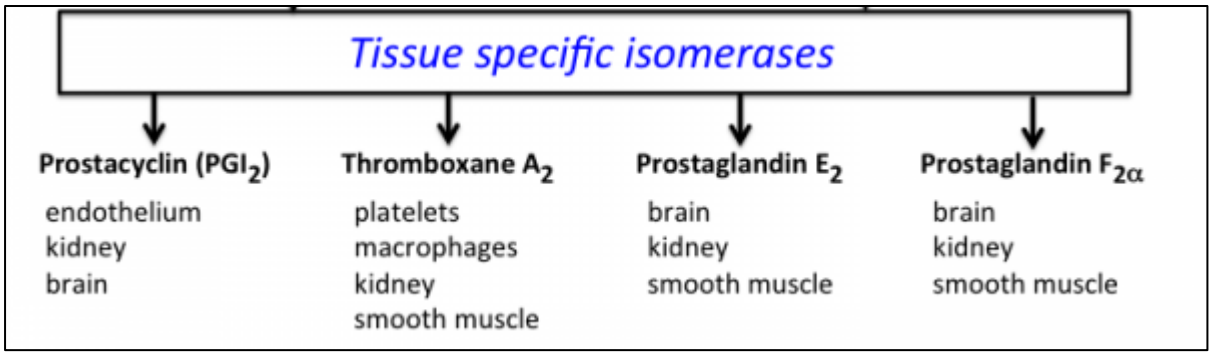

Figure 3: Prostaglandin isomerases specific to each tissue (Kawahara *et al.* 2015).

Many of the NSAIDs act nonspecifically on COX but more recently developed NSAIDs have been reported to act more specifically on the COX-2 isoenzyme, with the aim to decrease fever, pain and inflammatory response whereas reducing associated gastrointestinal and renal side-effects relating to COX-1 inhibition. According to recent studies, COX-2 selective agents such as Rofecoxib and Celecoxib can promote thrombosis and substantially increase the risk of heart attack (Serhan and Levy 2003). However, the pattern of toxicity is the same with COX-2 selective and COX non-

selective (e.g. aspirin) NSAIDs at overdose cases. These medicines act by binding to the active sites of COX and preventing the catalysis of arachidonic acid (AA) to prostaglandins therefore exerting analgesic, antipyretic, and anti-inflammatory properties (Hunter *et al*. 2011). The chronic use of NSAIDs at therapeutic doses is generally safe in patients with normal physiology and without any underlying problem. Toxicity associated with NSAIDs is result of excessive inhibition of COX-1 and eventually reduction in prostaglandin synthesis. Therefore, this condition can trigger organ damage such as gastrointestinal, renal and central nervous systems (CNS) as adverse effects both in therapeutic use and in acute overdose (Hunter *et al.* 2011).

Nephrotoxicity mechanisms of NSAIDs

NSAID-induced renal adverse effects are rare, sometimes temporary and usually reversible at the time of drug withdrawal. The occurrence rate and the seriousness of the renal effects raise in patients with risk determinants such as those who has diabetes, heart failure, cirrhosis, renal dysfunction, users of diuretics and in the elderly subjects. Unwanted effects extend from electrolyte retention and reduce glomerular filtration (by means of inhibiting vasodilator prostaglandins) to nephritic syndrome and chronic renal failure. While acetaminophen and aspirin may develop chronic interstitial nephritis, remaining NSAIDs may generate acute interstitial nephritis, altered intraglomerular hemodynamics, chronic interstitial nephritis and glomerulonephritis. The correlation has been found between high plasma concentration and the renal adverse effect of NSAIDs (Emkey *et al.* 1982). Early diagnosis is important because chronic interstitial nephritis has been known to progress to end-stage renal disease (Harirforoosh and Jamali 2009).

In cases of severe toxicity, detoxification and compensatory mechanisms are insufficient and an increase in rate of kidney insufficiency can be encountered. It has been reported that over 300 chemical substances including NSAIDs cause kidney damage and the incidence of drug-induced nephrotoxicity is as high as 66 % in elderly patients (Murray *et al.* 1971).

Nephropathy can be the result of oxidative stress, impaired membrane integrity, direct toxicity because of chromium or cadmium accumulation. While the different parts of nephron may be the targets of nephrotoxins, the proximal tubule is the most common target site of nephrotoxins, including the drugs (Murray *et al.* 1971).

Glomerular filtration is reduced because of the increase in the amount of tubular cell death. If this happens too many nephrons, the total glomerular filtration rate would

decrease and tubular cell loss leads to the abrasion of the basolateral membrane which would prevent clearance of compounds that are required to be removed from the body by urine. This may lead to acute renal failure within a few days. Severe DNA damage can also cause cell death. If DNA damage that is not very severe is repaired improperly, the remaining DNA lesions may lead to the formation of renal cancer over the years. Long-term treatment with opioid analgesics may not cause direct damage to the kidney. However, it may induce the infiltration of immunocytes to kidneys over a long time. While these immunocytes do not directly produce acute nephritis, the frequent use of these agents may gradually reduce renal function (Schrier 2013).

On the other hand, kidney has a great regeneration ability. Even if a large part of the proximal tubular cells is lost, the cells multiply within 1-3 days after the initial injury. The new cells are flat and within a few days they will differentiate into unique proximal tubule cell (Schrier 2013).

NSAIDs cause nephrotoxicity that can present as various renal syndromes such as acute kidney injury, nephritic syndrome, interstitial nephritis, and chronic renal failure (Figure 4). The common link among these various syndromes is the disruption of PG synthesis. The PGI2 has predominant vascular actions in the form of renal vasodilation. PGE2 has renal tubular action in the form of inhibition of salt and water reabsorption, especially in the thick ascending limbs of loop of Henle and collecting ducts (Schrier 2013).

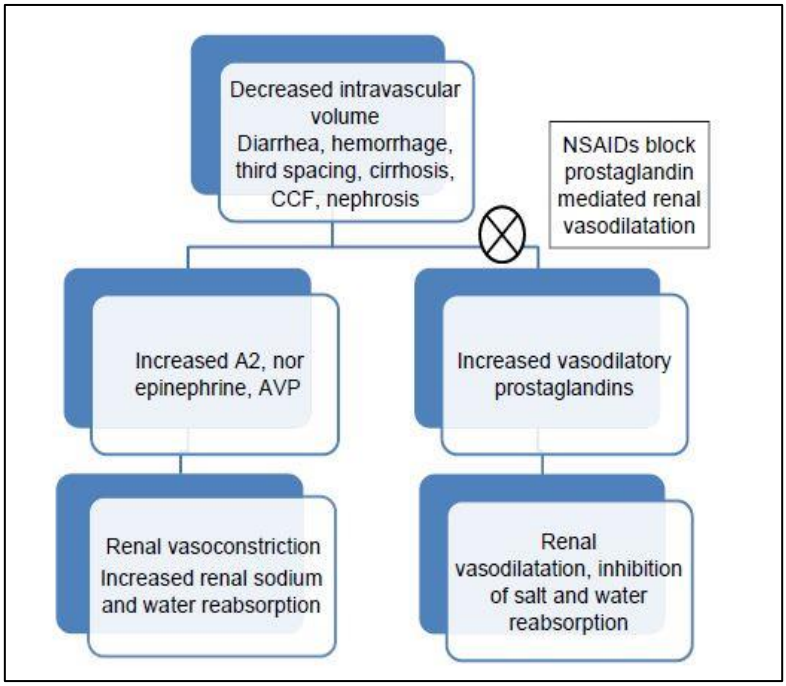

Figure 4: Mechanism of renal toxicity of NSAIDs (Schrier 2013).

These biological actions of the autacoids on the kidney are prominent in the setting of a decreased effective arterial blood volume during which there is an increase in the circulating levels of angiotensin II (AII), arginine vasopressin (AVP) and catecholamines. PGs, once released, act to counterbalance the effect of the abovementioned hormones by causing renal vasodilation and inhibition of salt and water reabsorption. Therefore, the inhibition of PG synthesis by NSAIDs (COX inhibitors) leads to the unopposed action of AII, AVP, and catecholamines, resulting in enhanced renal vasoconstriction and salt and water reabsorption. As the renal medulla is dependent on the production of PGs for its blood flow, the inhibition of PG synthesis by NSAIDs leads to medullary ischemia and papillary necrosis (Schrier 2013).

In order to comprehend the renal effects of NSAIDs, a brief knowledge of the physiologic function of eicosanoids in the kidney is essential. A composite term, eicosanoid, is the outcome of arachidonate or other polyunsaturated fatty acid metabolism and covers prostaglandins, prostacyclin, thromboxane, epoxides and lipoxygenase products. COX isoforms are responsible for this conversion and they are inhibited irreversibly by aspirin and reversibly by the remaining NSAIDs (Schrier 2013). There are four main areas within the kidney that are rich in the concentrations of both isoforms of COX; the afferent and efferent arterioles, interstitial cells of renal medulla, the glomerulus and medullary collecting ducts. Eventual products of the conversion are further metabolized to PGI_2, PGE_{2alpha}, PGD_2 and TXA_2. This suggests that each cell which has cyclooxygenase enzyme can create all types of eicosanoids, however one or two are predominant depending on the situation. Accordingly, arterioles produce PGI_2, glomeruli produce PGI_2, PGE_2 and TXA_2, and both interstitial cells and collecting duct cells produce PGE2. Both TXA_2 and PGH_2 have practically same actions and they activate a mutual receptor (Schrier 2013). Their binding ends up with phospholipase C stimulation, creation of inositol diacylglycerol and triphosphate, and super elevation of free cytosolic calcium derivatives from intra- and extracellular origins. Subsequently, smooth-muscle contraction and renin release inhibition are generated. In contrast, PGI_2, causes vasodilation and renin release stimulation by activating adenyl cyclase and raising intracellular cyclic adenosine monophosphate (Lote *et al.* 1989).

Phospholipase A_2 which is found in renal arterioles and is activated by circulating vasoconstrictors like angiotensin II and norepinephrine, leads to production of PGI_2, that adjusts renal vasoconstriction. The lipoxygenase juxtaglomerular specialized

smooth muscle cells release rennin when they are exposed to PGI_2. Glomerular originated synthesis of PGI_2, PGE_2 and TXA_2 are also stimulated by angiotensin II too (Schrier 2013). These three affect glomerular size: While PGI_2 and PGE_2 expands the glomerulus, TXA_2 leads to the contraction. They also affect ultrafiltration coefficient. TXA_2 which is formed in the glomerulus narrows the downstream efferent arteriole, intensifying the resistance and managing glomerular capillary pressure. Interstitial cells of deep renal medulla generate high amounts of PGE_2 when subjected to angiotensin II or vasopressin. Moreover, an increase in renal artery perfusion pressure provokes the increase of PGE_2 production. PGE_2 reduces sodium reabsorption in Henle's loop, hence undermining sodium retention of angiotensin II and subscribing to pressure natriuresis. Ultimately, when collecting duct cells are exposed to vasopressin, they produce PGE_2 and other eicosanoids (Fischer and Weber 1984).

To summarize, products of COX are formed in both renal cortex and medulla and the rate of their generation increases in response to particular stimuli. Once they are released, they affect renal hemodynamics, renin release, sodium and water excretion, erythropoietin production and aids natriuresis and diuresis (Fischer and Weber 1984).

Effects of NSAIDs on renal hemodynamics

There is a relationship between the level of plasma renin activity and the decline in renal blood flow after COX inhibition. As the pretreatment of plasma renin activity increases, the renal blood flow decreases after NSAIDs (Rossat *et al.* 1999).

In addition to the activation of the renin angiotensin system, other risk factors for NSAID-induced reduction of GFR may exist. Renal glomerular diseases such as; renal systemic lupus erythematosus and nephrotoxic serum nephritis are among these factors. Renal insufficiency caused by excision of renal mass is not affected by NSAIDs. Immune-induced glomerulopathy triggers vasodilator eicosanoid production, which manage GFR. It decreases if glomerular COX is inhibited. However, GFR is not reduce by NSAIDs in the absence of active glomerulonephritis because of not increasing vasodilator eicosanoids (Rossat *et al.* 1999).

Renal artery stenosis increases NSAID caused nephrotoxicity whereas, renin angiotensin system may trigger and support GFR in the stenotic kidney. However, their impacts in the no stenotic kidney is less presumable. NSAIDs could reduce contralateral blood flow because of lessen vasodilator eicosanoid formation or raise it by decreased renin release. So that, bilateral renal artery disease or renal artery stenosis in

a kidney might be a risk determinant for NSAID-induced renal failure (Rossat *et al*. 1999).

Progressive age is a dependent risk factor for NSAID-induced renal dysfunction. Prevalence of the activation of renin-angiotensin system by various factors increases in elderly people. These various factors include; congestive heart failure, diuretic usage, decreased thirst mechanism or atherosclerotic major renal vascular disease (Rossat *et al.* 1999).

To sum up, NSAIDs have little effect on renal blood flow of GFR in normal kidney. However, when the kidney is overexposed to vasoconstrictor stress, eicosanoid production is increased and this plays an important role in maintaining GFR. Similar case occurs during active glomerular inflammation and in the case of renal artery stenosis. Indomethacin can produce profound and prolonged depression of GFR (Loudon *et al.* 1997).

Effects of NSAID on renin release

There are two clinically convenient consequences of decreased renin release: Reduction of blood pressure and hyperkalemia. In many conditions, it is reported that NSAIDs either do not affect or nebulously increase the blood pressure. Nevertheless, since blood pressure and very high rennin plasma activity are dependent to each other, NSAIDs might reduce blood pressure indeed. The renal baroreceptor mechanism that leads to increased renin synthesis and release when renal perfusion pressure is deducted is enhanced by PGI_2 synthesis. Therefore, blood pressure reduce can be ensured by reducing renin by inhibiting COX. Another common and life-threatening condition is hyperkalemia (Harris 2003). Prolonged NSAID treatment increases serum potassium levels respectably that peaks at 3-7 days of treatment. Levels of potassium return to normal in 1 or 2 days after withdrawal of NSAIDs. Another risk factor for NSAID-induced hyperkalemia is diabetes mellitus where; there is a deficiency of insulin mediated cellular potassium reuptake and angiotensin-converting enzyme inhibitor treatment which reduces angiotensin II levels. As a result, NSAIDs continuously decrease basal and stimulated plasma renin activity and plasma aldosterone. In normal functioning kidneys, NSAIDs cause remarkable increase in serum potassium. In the case of renal insufficiency or renal insufficiency additional to diabetes mellitus, the extent of hyperkalemia turn out lethal conditions (Stichtenoth *et al.* 1998).

NSAIDs and sodium and water metabolism

Inhibition of renal PG synthesis can affect sodium excretion by various mechanisms which are shown in Table 1 (Hao *et al.* 2000). PGs have both direct and indirect effects on sodium excretion. Direct impacts

are supposedly restricted to the distal nephron, likely to the collecting duct epithelia. Indirect effects, running through hemodynamic and Starling forces, alterations in medullary interstitial pressure or salt content, varied concentrations of other determinants such as; angiotensin II and vasopressin may define the whole outcomes of NSAIDs on sodium metabolism. Depending on the potency of NSAID used, sodium excretion would increase, remain unaffected or decrease. In a research, it was reported that; 75 mg single dose of indomethacin lowered urine PGE_2 by 65% and urinary sodium from 200 to 125 mmol/day after 24 hours in high sodium diet and from 43 to 21 mmol/day in low sodium diet. In prolonged studies, indomethacin was reported to cause weight gain by 1 and 2% averagely but rarely up to 5%. Formed fluid retention is in charge of suppressing basal plasma renin activity. In patients with inherent renal disease or disorders where circulating vasoconstrictors are increased, NSAIDs withdrawal lead to fluid retention. Also, reductions in renal blood flow and GFR reduces the filtered load sodium. Water retention generating hyponatremia is occasionally an adverse effect of NSAIDs. However unexpectedly; PGE_2 inhibits the effect of vasopressin on the collecting duct and NSAIDs may increase the discharge of vasopressin during the volume contraction stimulus. Furthermore, decreasing medullary blood flow may lead to raised osmolality in the medulla and increased water reabsorption which can cause promoted water reabsorption from the collecting duct when administered NSAIDs actually causes serious hyponatremia. A study which was performed among normal subjects showed that 75 mg indomethacin for a week and for 42 days do not cause any change on serum sodium levels whereas, patients who were previously exposed to hyponatremia or those with severe congestive heart failure, cirrhosis with ascites, or who were taking diuretics or with nephrotic syndrome might possibly develop severe hyponatremia by the over usage of NSAIDs (Waddington *et al.* 2014).

Table 1: Possible effects of cyclooxygenase inhibition on sodium excretion.

Effect	Mechanism	Effect on sodium excretion
Renal blood flow	Proximal convoluted tubule reabsorption	decrease
Rennin	The ascending loop of Henle reabsorption	increase
Interstitial pressure	The ascending loop of Henle reabsorption	decrease
Medullary blood flow	Addition of Na to tubular fluid	increase
PGE effect on collecting tubules	Collecting duct reabsorption	decrease
Natriuretic effect of AVR	The ascending loop of Henle reabsorption	decrease

Effects of NSAIDs on other renal functions

As mentioned before, there is a direct relation between erythropoietin synthesis, PGE_2 synthesis and renal hypoxia. Hypoxia reduces adenosine triphosphate (ATP) which possibly prevent reacylation of arachidonic acid, subsequently allowing it to be more metabolized by COX, leading an increase in the production of PGE_2. PGE_2 increases cAMP by increasing the activity of adenyl cyclase and activates the phosphorylation of protein kinases (PKs). Transcription of erythropoietin gene can elevate during all stages. It is therefore probable that NSAID-induced deterioration of circulating erythropoietin may lead to anemia usually observed in patients having these drugs (Borda 1992).

DISCUSSION

This present review focused on renal toxic mechanisms induced by NSAIDs. NSAIDs induced nephrotoxic mechanisms including, effects of NSAIDs on renal hemodynamics, renin release and sodium and water metabolism were clarified. The use of NSAID for a long period of time and in large quantities results in the formation of renal papillary necrosis and interstitial nephritis. This pathological condition is called analgesic nephropathy. This review will raise awareness of the patients on the severity of the problem and the importance of reasonable and safe usage of NSAIDs. Adverse drug reactions of NSAIDs especially on kidney should never be underestimated for protection from serious irreversible risks.

Pharmacists and physicians should sufficiently be informed and be aware of the seriousness of analgesic nephropathy in order to avoid the unnecessary usage of NSAIDs, both with prescriptions and without prescription. The geriatric population is the most vulnerable group to toxic effects of NSAIDs. These people feel more pain and in order to reduce the pain they take NSAIDs in high doses for a long period of time. Moreover, geriatric individuals use many different drugs which

can show interactions with NSAIDs. Overall, this population should be well informed and monitored by healthcare professionals in order to decrease the risk of adverse related to NSAIDs.

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