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Review Article

Review on Effects of NSAID`S on Different Systems

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A B S T R A C T

Non steroidal anti-inflammatory drugs (NSAIDs) are amongst the most commonly prescribed medication. Some are available over the counter and likely to be abused. The gastrointestinal (GI), renal and cardiovascular (CV) side effects limit NSAIDs use. These side effects occurred at a rate as low as 1%–5% for NSAID users. The gastrointestinal (GI), renal and cardiovascular (CV) side effects limit NSAIDs use. Some studies have shown that an extra 2to8 per 1000 people per year may have a major vascular event from using an NSAID. Several studies demonstrated that conventional NSAIDs were associated with a higher risk of AKI and GN and decreased kidney hemodynamic functions, including sodium excretion. NSAIDs have a range of adverse effects mainly affecting the GI, renal and CV systems.

Keywords: Nonsteroidal, anti-inflammatory drugs, inflammation, cyclooxygenase enzymes

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INTRODUCTION

Non steroidal Anti Inflammatory Drugs is a class of Analgesic medication that reduces pain, fever and Inflammation. Non steroidal anti-inflammatory drugs (NSAIDs) are amongst the most commonly prescribed medication. Some are available over the counter and likely to be abused. Nonsteroidal anti-inflammatory drugs (NSAIDs) can induce kidney lesions.[1]Nephrotoxicity attributed to NSAIDS has been reviewed in the past.[2-8]The spectrum of nephrotoxicity includes acute tubular necrosis, acute tubulointerstitial nephritis, glomerulonephritis, renal papillary necrosis, chronic renal failure, salt and water retention, hypertension, hyperkalemia and hyperreninaemic hypoaldosteronism.[9] Most NSAIDs are acidic compounds with a relatively high bioavailability. They are highly bound to plasma proteins and are metabolized by the liver[10,11]. Glucuronidation by the kidney enzyme is also reported for some NSAIDs (e.g., naproxen, ibuprofen, ketoprofen) [11,12]. Most patients take therapeutic doses of these drugs for short durations and, usually, tolerate them well[13].The gastrointestinal (GI), renal and cardiovascular (CV) side effects limit NSAIDs use[14]. However, because NSAIDs are one of the most prescribed drugs and some of them are available over the counter, these small increased risks may translate into high absolute numbers of patients being affected, especially in those with preexisting impaired kidney function[15].

History

NSAIDs are very effective in the alleviation of pain, fever and inflammation, and millions of patients worldwide have found relief in their use since the discovery of the soothing properties of willow bark more than 3,500 years ago. These side effects occurred at a rate as low as 1%–5% for NSAID users[16].Compared with nonselective NSAIDs, selective NSAIDs tend to have less gastrointestinal side effects but more cardiovascular side effects. In 2004-2005, some selective (COX 2) inhibitors were withdrawn from the US market because of an increased risk of heart attack and stroke

in people who took them. In 2005, the US Food and Drug Administration (FDA) added a warning label to prescription NSAIDs about this increased risk of heart attack prescription and over-the-counter NSAIDs except aspirin in regard to the increased risk of heart attack and stroke.

Epidemology

Some studies have shown that an extra 2to8 per 1000 people per year may have a major vascular event from using an NSAID.The warning also notes that people given NSAIDs after a first heart attack were more likely to die in the first year after the heart attack compared with those who were not given NSAIDs and that there is an increased risk of heart failure with NSAID use. An attributable rate of hospitalisation greater than 1 per 100 patient years is unlikely,even in patients over 60 years of age. Based on a widely quoted population study,[17] it can be estimated that there are 8528 hospitalisations for gastric and duodenal ulcer bleeding per annum in the UK[18] Based on estimates that between 20% and 25% are causally associated with intake of non-aspirin NSAIDs, and approximately 10% more with aspirin used for cardiovascular prophylaxis, these figures suggest that (aspirin and nonaspirin)NSAIDs cause approximately 3500 hospitalisations for and 400 deaths from ulcer bleeding per annum in the UK in those aged 60 years and above[18].It is estimated that globally approximately seven billion dollars is spent on NSAIDs per year that makes upto 2.5% of all the prescription dollars in the world[19].Among various NSAIDs, diclofenac is the most commonly used NSAID worldwide[20].

Signs and Symptoms

Several studies demonstrated that conventional NSAIDs were associated with a higher risk of AKI and GN and decreased kidney hemodynamic functions, including sodium excretion. However, these adverse effects were not consistently seen for selective cyclooxygenase (COX)2 inhibitors [21-27]. Non-steroidal anti-inflammatory drugs (NSAIDs) are well recognised as causing peptic ulceration and ulcer complications,s perforation, sudden death with bleeding in the community, and any oesophageal ulcer deaths attributable to NSAIDs. As well as their effects on the upper gastrointestinal tract, NSAIDs can also cause lower intestinal haemorrhage or perforation[28] and may exacerbate colitis[29].In addition, common non-gastrointestinal adverse effects include the consequences of salt and water retention, renal failure, provocation of bronchospasm, and hypersensitivity reactions. Of these,the propensity of non-selective and selective NSAIDs to induce salt and water retention has received increasing attention[,30-34] as has speculation about antiplatelet effects.[35,36]Selective COX-2 inhibitors cause sodium and water retention, hypertension, and oedema, with effects broadly similar to those of non-selective NSAIDs when compared at equivalent doses.[37-41]Many epidemiological studies show that ibuprofen use is associated with a halving of ulcer complication rates compared with average expectation for NSAID users[42]

Classification of NSAID`S

NSAIDs are categorized in different ways such as classification based on chemical structure (i.e. Table 1)[43] or based on selective inhibition of cyclooxygenase enzymes (i.e. Table 2)[44]. The COX-2 selectivity of NSAIDs is reported differently depending on the method used. However, in general, NSAIDs are divided into two major groups: cyclooxygenase (COX) -2-selective inhibitors (COXIBs) and non-selective NSAIDs. Many NSAIDs have a chiral structure. Of those, only naproxen has been available as a single pharmacologically active enantiomer (Table 1). Other chiral NSAIDs are available as racemates with the main antiinflammatory and analgesic activities attributed to the S enantiomer[45]. Ibuprofen is available worldwide as the racemate but S-ibuprofen is also marketed in some countries. In humans, the R enantiomer of some of the chiral NSAIDs is metabolized to the S enantiomer[46]. In some species this enantiomeric inversion can be bidirectional[47].

Table 1: Chemical classification of NSAID`s

Group	Example(s)
Salicylates	Acetyl salicylic acid, Sulfasalazine
Propionic acid derivatives	Ibuprofen*, naproxen*,ketoprofen*, Flurbiprofen, fenoprofen, Oxaprozin.
Pyranocarboxylic acids	Etodolac* Tolmetin, diclofenac, Heteroaryl acetic acid, ketorolac*
Alkanones	Nabumetone
Indoleacetic,	Indomethacin, sulindac
Indeneacetic acids	Etodolac*
Oxicams	Piroxicam, meloxicam
Pyrroloppyrrole	Ketorolac* Mefenamic acid,
Fenamates	Meclofenamic acid
Diaryheterocycles (COXIBs)	Rofecoxib, celecoxib, veldecoxib, paracoxib, etoricoxib, lumaricoxib

*Chiral molecule Adopted from reference 145 with modifications.

Table 2: Ranking of selected group of NSAID`s based on their COX-1 or COX-2 selectivity

NSAID`s	**COX-1**
Ketorolac	1
Flurbiprofen	2
Ketoprofen	3
Indomethacin	4
Acetylsalicylic acid	5
Naproxen	6
Tolmetin	7
Ibuprofen	7
NSAID`s	**COX-2**
Rofecoxib	1
Etodolac	2
Meloxicam	3
Celecoxib	4
Diclofenac	5
Sulindac	6
Meclofenamate	7
Piroxicam	7
Diflunisal	8
Sodium salicylate	9
Adopted from Reference 146 with modifications	

Therapeutic Use of NSAID`S

NSAIDs are used to relieve pain and discomfort associated with chronic conditions such as rheumatoid arthritis (RA) and [48] osteoarthritis (OA)[49]. Some of NSAIDs, including ASA, are also indicated for other disease states such as juvenile arthritis fever, thrombosis, pericarditis, Kawasaki disease, gout, gouty arthritis, ankylosing spondylitis, patent ductus arteriosus and dysmenorrhea[50]. They are also used to prevent colon cancer[52] and Alzheimer's disease[51] although their latter action has not been unequivocally confirmed[53].

Mechanism of Action of NSAID`S

The mechanism of action of NSAIDs was first described in 1971 by Vane and Piper who demonstrated that NSAIDs actually exert their effects through inhibition of prostaglandin and prostanoids biosynthesis by COX enzymes[54]. Prostanoids including prostaglandins (PGs), prostacyclins and thromboxanes are inflammatory mediators that are derived from arachidonic acid in a series of reactions known as arachidonic acid cascade[55]. COX isozymes are the first to convert arachidonic acid to prostaglandin (PG) G2[56]. Then, peroxidase metabolizes PGG2 to PGH2 which is, in turn, converted by tissue-specific isomerases to primary prostanoids including PGD2, PGE2, PGF2α, PGI2, and thromboxane A2.

Adverse Effects of NSAID`S

NSAIDs have a range of adverse effects mainly affecting the GI, renal and CV systems[57]. However, the majority of the patients taking therapeutic doses of these NSAIDs and for shorter duration usually tolerate them well[58]. However, with longer duration of treatment and in the presence of comorbidities higher risk may emerge.

Gastrointestinal Side Effets

Minor:

The most common side effect of NSAIDs is reported to be mild events such as dyspepsia,heartburn and nausea[59]. Most of these GI adverse effects are limited to the upper GI tract.The effectiveness of various gastro-duodenal-protective approaches to control upper GI side effects of NSAIDs has been reported[60-64].

Major:

This harmful effect of NSAIDs may result in serious conditions[65] that range from lesions to stricture of the lumen called the diaphragm disease[66]. All NSAIDs may casus the distal GI side effect although with varying intensity [67,68.]

Renal Side Effects

It is estimated that 1-5% of NSAIDs users may develop renal adverse effects[69]. Both acute (ARF) and chronic (CRF) renal failure can be caused by NSAIDs[70].Various forms of renal failures caused by NSAIDs have been observed including acute deterioration of renal function, renal papillary necrosis, acute interstitial nephritis, hyperkalemia and sodium and fluid retention[71,72]. Acute forms of these side effects are dose/duration-dependent and usually reversible. All major prostanoids including [73]. Both PGE 2 and PGI2 are important in renal function [74]. PGE2 which is located in nephrons, the renal medullary interstitial cells and the collecting tubules, is a vasodilator and plays a major role in excretion of salt and water by the kidney. Nevertheless, no NSAID can be assumed to be free of renal failure, at least, the acute type. It is important to emphasize that other analgesics such as aceetaminophen are also associated with renal failure [69.]

Acute Renal Failure

This side effect is typically dose and duration-dependent and reversible. Physical examination, laboratory data (e.g., an increase in serum creatinine), ultrasonographic and radiological tests can be utilized to diagnose ARF [75]. The use of NSAIDs can cause ARF by inhibiting production of PGs and consequently reducing the blood flow to the kidneys [75] and/or induction of interstitial nephritis [72].

Renal Papillary Necrosis

Renal papillary necrosis is a destruction of some parts or all renal papillae (RPN) [69]. NSAIDs may induce RPN by abruption of the blood flow to papillae and intensifying hypoxia present in papillae. Some cases of RPN have also been reported for several traditional NSAIDs and celecoxib.

Nephrotic Syndrome with Acute Interstitial Nephritis

Inflammation in the spaces between kidney tubules is the underlying mechanism of developing acute interstitial nephritis (AIN) [69]. Hypersensitivity to drugs, sepsis, and glomerular diseases can cause AIN [76]. The incidence of AIN is rare. It occurs days after exposure and is reversible. Nephrotic syndrome is presented with edema, oliguria, and foamy urine [69]. Hematuria and proteinuria can be observed as well. Due to inhibition of cyclooxygenase, an increase in production of other arachidonic cascade products (e.g., leukotrienes) can be responsible for induction of nephrotic syndrome by NSAIDs

Electrolyte and Fluid Retention

Sodium retention that occurs in 25% of patients exposed to NSAIDs [77] causes edema and weight gain [78]. NSAID-induced sodium retention may be the result of increases in the expression of the Na-K-2Cl co-transporter [79] which plays a role in excretion of sodium and maintaining the GFR [71]. All NSAIDs have been reported to cause peripheral edema [80,81]. It has been suggested that the acute sodium retention by NSAIDs in healthy of GFR is due to inhibition of COX-1 [80,81]. an inhibition of PGI2 production by NSAIDs may result in hyperkalemia [82]. Regardless of the COX-2 selectivity, NSAIDs have been associated with hyperkalemia [83,84] certain NSAIDs made patient more prone to development of hyperkalemia. In that study, the use of rofecoxib, celecoxib, diclofenac or indomethacin was associated with the highest risk of hyperkalemia. However, the incidence was not correlated with COX-2 selectivity.

Chronic Renal Failure

Chronic renal or kidney failure occurs when an assault, disease or toxins, damage the kidneys resulting in inadequate removal of fluids and wastes. Although rare, NSAIDs cause CRF secondary to interstitial nephritis or papillary necrosis. CRF can be an end-stage disease. The risk of CRF is increased in patients who have experienced ARF. Based on retrospective studies, some authors Eg[85] have suggested that NSAIDs with long half-life may demonstrate a greater risk of CRF due to their sustained inhibition of PG. It is evident that chronic use of any NSAID can cause CRF in some patients despite the data suggestive of safety if the population mean is considered Eg[86].

Hypertension Caused By Electrolyte Retention

It is generally believed that NSAIDs increase blood pressure, especially in hypertensive patients[87]. They can increase blood pressure by several mechanisms including retention of salt and fluid [88-90].

Summary of NSAID`S Renal Effects

The use of all NSAIDs has been associated with dose-dependent renal side effects with various etiologies. Many of the side effects are short-term and reversible upon NSAID withdrawal. Chronic use of NSAIDs, although relatively free of renal side effects in average patient, in some, particularly those with other risk factors and/or on other drugs such as diuretics and angiotensin inhibitors, may result in end-stage chronic renal disease. However, for the majority of patients, renal side effects of NSAIDs are rare particularly if they avoid high therapeutic doses.

Cardiovascular and Cerebrovascular Effects of NSAID`S

the CV complications have been highlighted as another major stumbling block against the use of NSAIDs. A confounding factor in identifying the latter side effects of NSAIDs has been the CV complications that have been known to be associated with the very disease that these drugs are indicated for; i.e., both the inflammatory conditions and NSAIDs may result in CV complications. Forman et al.[91] have suggested that the frequency of nonnarcotic analgesic use (including all NSAIDs and acetaminophen) is independently associated with a moderate increase in the risk of hypertension. Inflammatory conditions, such as arthritis, adversely influence the CV system so that patients with arthritis are afflicted with CV conditions to a significantly greater extent than the general population [92,93]. Furthermore a decrease in the pharmacological effect of some drugs, particularly those to treat CV complications, is also observed in inflammation. This adds another risk factor for increased CV outcomes in the patients under treatment with NSAIDs for their arthritis [94].

Dose Dependency of CV Side Effects

In a cohort study of patients with chronic heart failure, the hazards ratios for CV toxicity increased by NSAIDs use regardless of COX selectivity in a dose-dependent fashion [95]. Another report [96] that has received criticisms [97-99] suggests ibuprofen increases the risk of CV toxicity at high doses due, presumably, to the lack of antithrombotic effect of high doses. Low doses of ibuprofen may even have cardioprotective effects as suggested by Fosbol et al [100]. Naproxen also appears to be cardioprotective in low doses but neutral in high doses [100]. Likewise, higher doses of diclofenac, celecoxib, and rofecoxib were correlated with higher risk of MI or death [101.] According to a more recent review, celecoxib and ibuprofen have elevate CV risks in high doses used for clinical trials, but not in low doses as mostly used in clinical practice [102].Another study [103] suggests that the use of NSAIDs including rofecoxib is associated with only a small elevation of acute MI risk. The magnitude of the CV risk, however, increased by higher doses for all tested NSAIDs except for diclofenac. In the elderly, it appears that the first time MI risk increases with the use of rofecoxib in a dose-dependent manner [104].

Risk of Cardiac Death,All Cause Mortality

In the elderly, the issue of death due to NSAIDs use is controversial. In a nested case-control study conducted on the Australian veterans, Mangoni el at., reported a reduction in all-cause mortality reported for all NSAIDs regardless of their COX selectivity (OR 0.87, 95% CI 0.85, 0.90). The risk of death was also inversely associated with the number of prescription supplies [105]. Kerr et al. measured all-cause mortality outcome in the users of NSAIDs also in the Australian veteran population. They reported an elevated risk of death due to CV complications in the users of NSAIDs regardless of their COX selectivity [106]. As compared to the non-NSAID treatments, they noticed the highest hazard ratio for all non-selective NSAIDs (1.76; 95% CI, 1.59 - 1.94)

followed by rofecoxib (1.58; 95% CL, 1.39 - 1.79), meloxicam (1.49; 95% CI, 1.25 - 1.78), diclofenac (1.44; 95% CI, 1.28 - 1.62) and celecoxib (1.39; 1.25 - 1.55). Fosbol et al. estimated the risk of CV death associated with NSAIDs as composite event of coronary death, MI and stroke in a Danish Nationwide cohort that consisted of 4,416,807 individuals aged 10 years or older. The use of diclofenac (OR 1.91, 95% CI 1.62-2.42) and rofecoxib (OR 1.66, 95%CI 1.06-2.59) was associated with higher risk of CV death. In addition, ibuprofen increased the risk of CV toxicity at high doses. According to the authors, this could be due to the lack of antithrombotic effect at high doses. Higher doses of diclofenac, celecoxib, and rofecoxib were correlated with higher risk of death/MI. The possibility of death caused by NSAIDs in young and apparently healthy subject has been studied by Fosbol et al. [107] who presented the most striking data on the harmful effect of short periods (9–34 days) and often low doses of NSAIDs in a large Danish population of 10 years and older individuals with median age of around 40 years. They studied death and MI within a nine-year follow-up period. They found no significant difference in risk associated with the first few days of treatment compared with the rest of the treatment interval. Even more interesting than Fosbol et al.'s observation [107] is the report of Goodson et al. that, through a population based study consisting of 923 inflammatory polyarthritis patients from the UK Norflok Arthritis Register (NOAR), suggest no increase in the risk of death for the users of NSAIDs and instead an inverse association between all-cause mortality and CV mortality. It is generally believed that certainly rofecoxib and probably diclofenac use are associated with CV events. There is no consensus, however, to extrapolate the observation made on the above NSAIDs to the entire class of compounds.

Risk of Myocardial Infarction

Amongst the CV conditions associated with NSAIDs, MI is the most studied, due, perhaps, to being more lethal and most common. Most studies have reported the risk associated with all NSAIDs with varying intensity, dose and duration [102]. The mechanism of the CV effect of NSAIDs is unclear but, at electrophysiology level, Grimaldi-Bensouda et al. have found that the MI risk modification associated with NSAID is limited to non-ST elevation [108]. retrospective cohort studies suggest an increased risk for CV outcome even with non-selective NSAIDs such as diclofenac and ibuprofen [109-111]. Others also reported no cardioprotective effects for any tested NSAID contrary to what previously noticed for naproxen and indomethacin [112-114]. A recent meta-analysis of the major randomized controlled trials on the effect of NSAIDS has concluded that, except for naproxen, NSAIDs used commonly in clinical practice are associated with increased risk of acute MI at high doses or in the patients previously diagnosed with coronary heart disease. For diclofenac and rofecoxib, the risk is elevated for both low and high doses [115]. The use of rofecoxib was associated with higher risk (RR, 1.24; 95% CI, 1.05-1.46) as compared with that of celecoxib and no NSAID [116].The use of rofecoxib was associated with higher incidents of acute MI (RR, 3.30; 95% CI, 1.41 - 7.68; p = 0.01). Although celecoxib did not increase the risk of acute MI (RR, 1.44; 95% CI, 0.57 - 3.69; p = 0.44), it significantly elevated the risk of stroke (RR, 2.43; 95% CI, 1.05 - 5.58; p = 0.04). The use of all NSAIDs caused hemorrhages, however, it was more severe in celecoxib and rofecoxib groups [117]. 365,658 subjects aged 40-85 in Canada 109. The use of celecoxib, rofecoxib, diclofenac, naproxen, ibuprofen, or indomethacin was associated with a small elevation of acute MI risk (5.1/1000 person/year). A dose-related death due or re-infarction has been reported in the Danish population who used NSAIDs [118]. It has been intuitively believed that the CV risk associated with NSAIDs is greater with their long term use (18 months) as it has been observed in the APPROVe trial [119] until recently, when a cohort study from Europe reported that even a short term use of NSAIDs by patients with a history of MI increases the risk of death and MI [120]. The history of previous MI on the CV risk of NSAIDs has been investigated. A group of researchers have reported[121], in the elderly currently on rofecoxib and with no history of MI, an evidence of an increased risk of acute MI which increased at higher doses.These authors detected no increased risk with celecoxib or other NSAIDs. Interestingly, according to these investigators, ASA use reduces the risk associated with low-dose but not high-dose rofecoxib. 3,293 patients taking NSAIDs for OA (the LOGICA study) observed a high risk of CV among the patients (44% of patients)[122]. A high risk of CV toxicity was noticeable among patients with previous MI after short and long term NSAID therapy [123].A dose-related death due or re-infarction has been reported in the Danish population who used NSAIDs[124]. The authors concluded that all doses of celecoxib and rofecoxib but only high doses of non-selective NSAIDs dosages increase mortality in patients with previous MI. They suggested that these drugs should, therefore, be used with particular caution in these patients. A dose-related death due or re-infarction has been reported in the Danish population who used NSAIDs[124]. The authors concluded that all doses of celecoxib and rofecoxib but only high doses of non-selective NSAIDs dosages increase mortality in patients with previous MI. They suggested that these drugs should, therefore, be used with particular caution in these patients. However, the risk of acute MI was higher among patients using higher doses of rofecoxib (>25 mg/day) compared to patients using higher doses of celecoxib (>200 mg/day)"[125].Rofecoxib appears the most toxic of all tested NSAIDs while naproxen and etodolac may be the safest.

Risks for Cardiogenic Stroke

The effect of NSAIDs on the risk of stroke has been evaluated by several investigators. A retrospective cohort study of subjects aged 50 to 84 years old showed an increase in risk of stroke among those who took rofecoxib or valdecoxib but not in those on several non-selective NSAIDs (diclofenac, ibuprofen, naproxen, and indomethacin)[126]. In contrast, another retrospective cohort study of 162,065 Australian veterans found that, except for ibuprofen, both non-selective (naproxen, indomethacin, piroxicam, meloxicam, and diclofenac) and COXIBs (celecoxib and rofecoxib) increased the risk of stroke[127]. Another retrospective nested case control study carried out on the Australian veteran population suggests no increased risk of stroke in non-selective NSAIDs users[128]. In a meta-analysis of 31 trails comparing NSAIDs with placebo, ibuprofen was associated with the highest risk of stroke (3.36; 95% CI, 1.00-

11.6) followed by diclofenac (2.86; 95% CI, 1.09-8.36), etoricoxib (4.07; 95% CI, 1.2315.7) and diclofenac high dose (3.98; 95% CI, 1.48-12.7)[129].Yet in another study pooled RR of stroke was higher for rofecoxib (1.64; 95% CI, 1.15-2.33) and diclofenac (1.27; 95% CI, 1.08-1.48) but not for naproxen, celecoxib, ibuprofen[130]. Another study suggests a 1.88 times increased risk of stroke (95% CI, 1.70–2.08) in general population using NSAIDs[131]. No clear conclusion can be made regarding the possibility of an increased risk of stroke in the users of NSAIDs as the literature that is all based on historical evaluations, is highly controversial.

Risk of Thrombotic Event

The outcome of the most of the clinical trials suggests a positive association between the use of NSAIDs and increased thromboembolic events regardless of their COX-2 selectivity[132,133]. The mechanism behind this effect of NSAIDs which has been known for decades is their ability to interfere with the prostacyclin pathway.small increase in the rate of cerebrovascular thromboembolic events in users of celecoxib compared to meloxicam but not in the rate of CV thromboembolic or peripheral venous thrombotic events[134].A small relative increase in the rate of cerebrovascular thromboembolic events and a relative reduction in peripheral venous thrombotic events in users of rofecoxib as compared with meloxicam. They, however, noticed no difference in the incidence of CV thromboembolic events between the users of rofecoxib and meloxicam[134].

Risk of Atrial Fibrillation

Multiple studies indicate an elevated risk of atrial fibrillation (AF) associated with the use of NSAIDs [135-137]. The risk was higher among the patients who took NSAIDs for more than one year. a larger cohort study consisting of 7,280 Taiwanese patients diagnosed with AF and 72,800 controls evaluated the exposure of patients to non-selective (ketorolac, ketoprofen, ibuprofen, etodolac, diclofenac, indomethacin, sulindac, piroxicam, meloxicam, naproxen, fenoprofen, flurbiprofen, tenoxicam, mefenamic acid, meclofenamic acid, flufenamic acid and tolfenamic acid) or COXIBs (celecoxib and rofecoxib) and the risk of AF[136].Investigators reported a high risk of AF for new users of non-selective but not for patients who took COXIBs. In contrast, a population based case-control study suggested an increased risk of AF for new users of NSAIDs regardless of their COX selectivity[137]. Since there may be a relationship between inflammation and AF, Hobach et al.[138]hypothesized that the use of the antiinflammatory naproxen in post-operative patients may reduce the incidence of AF. The use of naproxen failed to reduce the incidIt appears that NSAIDs increase the incidence of AF despite their antiinflammatory propertiesence of AF but decreased its duration in a limited sample of the patients.

Risk of Elevated Blood Pressure and Hypertension

The NSAIDs induced electrolyte imbalance, coupled with NSAIDs inhibitory effect on the production of vasodilator prostacyclin (PGI2)[139], results in increased blood pressure, hypertension and consequently, CV complications. Yu, et al.[140] have shown that a blockage of vascular COX-2 results in a lower PGIM in the urine predisposing the animal to both hypertension and thrombosis. Moreover, blockade of vascular COX-2 is linked to a lower endothelial NO synthase suppression of PGI2 which is likely to augment the already compromised blood pressure homeostasis. Another study has suggested the hardening of arteries as the mechanism for increased peripheral resistance caused by NSAIDs that results in hypertension and serious CV event[140].As compared with acetaminophen, first prescription of NSAIDs moderately increases systolic blood pressure by 2 mm Hg in patients with hypertension with a great data variability (95% CI, 0.7 - 3.3). However, NSAIDs fail to influence blood pressure in patients who are concurrently taking diuretics or those who use combinations of two or more antihypertensive medications.Compared to naproxen, ibuprofen is associated with a 2.5 mmHg increased systolic blood pressure (95% CI, 0.5 - 4.6).In addition, ibuprofen is associated with a clinically important increased systolic blood pressure with a risk factor of 1.47 (95% CI, 1.09 - 1.96). Compared to ibuprofen or naproxen, celecoxib is not associated with a clinically important increase in systolic blood pressure[141]. Krum et al. reported that etoricoxib is associated with higher systolic ($p < 0.0001$) and diastolic blood pressure ($p < 0.0001$ to $p = 0.0015$) compared to diclofenac[142]. Likewise, naproxen is also reported to cause elevation of blood pressure in a randomised control trial of 916 patients[143]. Others have concluded that all selective and nonselective NSAIDs have the ability to disrupt the blood pressure homeostasis with varying degree[144].

CONCLUSION

NSAID`s are used by several number of people diagnoised with arthritis and other diseases to reduce inflammation and pain associated with this type of diseases. These are very potent and causes many side effects like GI (major and minor), Renal, CV Implications, which are rare but serious.Low doses of NSAID`s are safe for patients who donot have Renal or CV comorbidities. They have potential of causing GI damages, mainly in lower parts of the tract,regardless of mechanism of action,D ose, and formulation. The use of GI protective drugs such as Mesoprostol along with NSAID`s for patients at risk of GI complications is also advicable and benificial. Non NSAID Analgesics such as Acetaminophen, and Antiinflammatories like Glucosamine have safety profile. Topical NSAID`s have lower systemic exposure (lower absorption from systemic circulation) when compared with oral doses, they may be expected to cause less side effects, but topical use of NSAID`s have possibilities to cause skin rashes. To minimize the CV effects of selective COX-2 inhibitors, investigators have suggested targeting the TXA2 receptor to balance the undesired CV effects of NSAIDs. Pharmacogenetics have role in CV complications of NSAID`s. Safe antiinflammatory drugs should be broadened to the molecular level and cover various receptors involved in the side effects and also to explore pharmacokinetic and drug delivery potentials.

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