

Adverse Cardiovascular Events by Non-Steroidal Anti-Inflammatory Drugs

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Abstract

Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) are medications widely used to relieve pain and to reduce inflammation. Like any medication, NSAIDs have potentially adverse effects that must be considered with their benefits.

Objective: To overview the cardiovascular adverse events that are associated with using NSAIDs in patients with and without history of cardiovascular diseases, and to identify the patients that are in the highest risk for cardiovascular complications.

Methods: Reviewing the recent literature and studying the related topics; data abstraction and connecting the findings and summarize them.

Results: There is increase in the risk of cardiovascular events associated with the use of NSAIDs. Nonselective and selective cyclooxygenase-2 (COX-2) NSAIDs are associated with an increased risk of atherothrombotic events. Celecoxib and rofecoxi are selective COX-2 inhibitors that are responsible for a significant risk of cardiovascular thrombotic events. Some NSAIDs, such as ibuprofen, indomethacin, and naproxen increase the mean arterial pressure in hypertensive patients. The risk of heart failure is doubled by all NSAIDs, and the current users have a higher risk of heart failure than chronic users. Additionally, NSAIDs may induce atrial fibrillation, and the risk is doubled in patients with heart failure.

Conclusion: NSAIDs can cause a lot of cardiovascular adverse events, such as heart failure, myocardial infarction, congestive heart failure, hypertension, atrial fibrillation, and can even lead to death. Therefore, NSAIDs should be used at the lowest effective dose for the shortest possible duration of therapy, especially in the elderly and patients at high risk for an adverse event.

Keywords: NSAIDs; Cardiovascular Effects; COX Inhibitors

Abbreviations

NSAIDs: Nonsteroidal Anti-Inflammatory Drugs; COXs: Cyclooxygenase; GI: Gastrointestinal; RCTs: Random Clinical Trials; PPIs: Proton Pump Inhibitors; CHF: Congestive Heart Failure; MI: Myocardial Infarction; AMI: Acute Myocardial Infarction; CVDs: Cardiovascular Diseases; SBP: Systolic Blood Pressure; CCB: Calcium Channel Blocker; AF: Atrial Fibrillation; CABG: Coronary Artery Bypass Grafting

Introduction

Drugs can be classified in different ways according to their mode of action, indications, and chemical structure. Nonsteroidal anti-inflammatory drugs (NSAIDs) are medications that are widely used to relieve pain and to reduce inflammation. NSAIDs are among the most common pain relief medicines in the world. Although these drugs are very effective, they could be associated with many side effects that sometimes can be serious. Many of these side effects may be prevented by careful consideration of the patient's risk factors [1,2].

The principle mechanism of action in the pharmacodynamics and toxicodynamics of NSAIDs is inhibition of cyclooxygenase (COX). There are two isoforms of COX: COX-1 and COX-2 enzymes. This enzyme generates inflammatory mediators of the prostaglandin group which are chemical messengers that mediate inflammation, fever and the sensation of pain [3].

Biosynthesis of prostaglandins is significantly increased in inflamed tissue and they contribute to the development of the cardinal signs of acute inflammation [4]. Prostaglandins play important roles in many cellular responses and pathophysiologic processes, such as modulation of the inflammatory reaction and its resolution, erosion of cartilage and juxta-articular bone, gastrointestinal cytoprotection and ulceration, angiogenesis and cancer, hemostasis and thrombosis, renal hemodynamics and progression of kidney disease, as well as atheroprotection and progression of atherosclerosis [5].

In general, COX-1 enzymes are widely distributed in the body, but most are concentrated in cells of the stomach, kidney, endothelium, and platelets. COX-1-dependent prostanoids play an essential homeostatic role in physiological functions (such as provide gastroprotection by regulating mucous secretion, control renal perfusion, promote platelet aggregation, vascular smooth muscle tone modulation, and anti-thrombogenesis) [6,7]. On the other hand, COX-2, which is induced by inflammation, is present in macrophages, leukocytes, fibroblasts, and synovial cells [6]. COX-2-dependent prostanoids have a role in mediating pain, inflammation, fever, as well as inhibiting platelet aggregation. Additionally, they can play dominant roles in pathophysiologic processes such as cancer, and physiological processes such as endothelial vasoprotection [3,7]. These two cyclooxygenase isoforms (COX-1 and COX-2) are the targets of nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs are competitive active site inhibitors of both COXs; both therapeutic and adverse effects of NSAIDs are mainly due to the inhibition of prostanoid biosynthesis [7,8].

Selectivity of NSAIDs

NSAIDs are classified according to their mechanism of action into nonselective and selective NSAIDs. Nonselective NSAIDs, such as ibuprofen and naproxen, inhibit both COX-1 and COX-2 enzymes. Selective NSAIDs, also known as coxibs, such as celecoxib and rofecoxib, target the COX-2 pathway only. Another class of semi selective NSAIDs (indomethacin, meloxicam, and diclofenac) has a higher affinity to COX-2 enzyme but at the same time tend to inhibit the COX-1 pathway [9].

COX-isozyme selectivity of NSAIDs plays a major role in determining the relative gastrointestinal and cardiovascular risks [10]. Many adverse effects are caused by inhibition of COX-1, while most of the therapeutic effects are caused by inhibition of COX-2 [5]. Therefore, drugs with low potency against COX-1 and a lower COX-2/COX-1 activity ratio will have anti-inflammatory activity with fewer side effects. Besides, NSAIDs with a longer half-life may be associated with an increased propensity to cause adverse effects [11].

Adverse effects

Like any medication, the potential adverse effects of NSAIDs should be considered with its benefits. Using NSAIDs is associated with a broad spectrum of side effects including ulcers, bleeding, kidney failure, and increased risk of heart attack and stroke [12,13].

Gastrointestinal effects

The main risk factors for NSAID-related gastrointestinal (GI) complications are old age (especially ≥ 70 years), prior uncomplicated or complicated ulcer, concomitant use of other drugs (including aspirin, other nonaspirin antiplatelet agents, anticoagulants, steroids or selective serotonin reuptake inhibitors), severe illness, alcohol and tobacco use, and *Helicobacter pylori* infection [14].

There is a systematic review of random clinical trials (RCTs) which concluded that COX-2 inhibitors can significantly reduce the risk of perforation, obstruction, and bleeding compared with nonselective-NSAIDs plus proton pump inhibitors (PPIs). However, this benefit was significant only for high-risk and long-term users [15].

Renal effects

NSAIDs can cause two different forms of renal failure. They can cause hemodynamically mediated failure (due to a decrease in prostaglandin synthesis induced by the NSAIDs) and acute interstitial nephritis (due to direct toxicity of the NSAIDs on the renal parenchyma) [16].

Hepatic effects

Elevation of liver enzymes can occur with the use of NSAIDs. There are some rare cases of liver failure as a result of NSAIDs. Most NSAIDs are documented to cause liver injury, and the damage tends to be hepatocellular in nature [17].

Hematologic effects

Hematologic side effects from NSAIDs are primarily related to their antiplatelet activity. Long-term use of low dose aspirin is enough to block platelet thromboxane A₂ production by more than 95% and to inhibit platelet aggregation. For this reason, it is recommended to stop aspirin and aspirin-containing medications 7 to 10 days before surgery in patients who are not at high risk cardiac events and are undergoing a noncardiac procedure [18].

Adverse effects of NSAIDs on the cardiovascular system:

NSAIDs affect the cardiovascular system in different ways. In atherosclerosis, which is a process with inflammatory features, selective cyclooxygenase 2 (COX-2) inhibitors may potentially have antiatherogenic effects by inhibiting inflammation. However, by decreasing vasodilatory and antiaggregatory prostacyclin production, COX-2 antagonists may lead to increased prothrombotic activity that can worsen and even cause heart failure, increased blood pressure, and increased risk of cardiovascular disease [19]. All cyclooxygenase (COX)-2 selective inhibitors (coxibs) appear to increase cardiovascular risk [20]. Several meta-analyses and systematic reviews indicate that diclofenac has demonstrated the highest cardiovascular risk of any of the nonselective NSAIDs [21]. A study was done to conclude that celecoxib and etoricoxib are related to a significant increase in cardiovascular risk, and they recommend to use these two drugs at a lower dose when NSAID use is necessary [21]. Analyzed clinical trials found that celecoxib and rofecoxib are two selective COX-2 inhibitors associated with increased risk of cardiovascular thrombotic events, such as myocardial infarction or unstable angina compared to naproxen, a nonselective COX inhibitor [19]. Naproxen is one of the least likely NSAIDs to increase cardiovascular risk in contrast to diclofenac and celecoxib which may be the most likely to increase cardiovascular risk. This is because, in contrast to non-aspirin NSAIDs, naproxen strongly inhibits platelet COX-1 activity, therefore inhibiting platelet aggregation [22]. Additionally, naproxen does not increase systolic blood pressure [23], but it appears to be among the NSAIDs that are more likely to damage the kidneys [24]. Other studies found that there is no evidence to support a reduction in risk of myocardial infarction associated with the current use of naproxen [25]. Meta-analyses of randomized clinical trials (RCTs) and observational studies have shown that COX-2 selective and nonselective NSAIDs are associated with an increased risk of atherothrombotic events (particularly acute myocardial infarction), with no significant difference in the incidence of vascular events between selective and nonselective agents (except for naproxen). The risk of cardiovascular events depends on the dose, duration, and frequency of NSAIDs administration. The use of both subclasses of NSAIDs can lead to the development of congestive heart failure (CHF) and increase the risk of dysrhythmia [26].

Patients with recent bypass surgery, unstable angina, myocardial infarction (MI), ischemic cerebrovascular events, or any other active atherosclerotic process with concurrent usage of NSAIDs are considered at a high risk of cardiovascular events, especially cyclooxygenase-2 (COX-2) selective agents [27]. Also, NSAIDs can increase the risk of new cardiovascular events in patients with heart disease [28].

NSAIDs and combination with other drugs should be considered. For example, using NSAIDs in elderly patients who are taking diuretics can cause a 2-fold increase in the risk of hospitalization for CHF. The interaction between diuretics and NSAIDs is well known. NSAIDs inhibit the synthesis of renal prostaglandins, which can have serious effects on renal function [29].

NSAIDs are one of the most common classes of medication used worldwide. As the aging population increases, the prevalence of painful arthritic conditions parallels. This could result in increases in the use of NSAIDs. Selective and nonselective cyclo-oxygenase inhibitors should be avoided [30]. Pharmacokinetic characteristics of NSAIDs as short half-life and a high degree of binding to blood plasma albumins are indicative of greater safety of NSAIDs [31], so in those patients NSAIDs should be given if necessary and must be used at the lowest possible effective dose for the shortest duration for the given indication [28], especially in patients with underlying atherosclerotic coronary disease [30]. NSAIDs are the leading cause of drug-related morbidity, especially in the elderly and patients with comorbidities. Most adverse effects are related to generalized inhibition of the major targets of NSAIDs: cyclooxygenases 1 and 2 [32]. The physiological changes of aging worsen the side effects profile of NSAIDs [33]. A study found that the recent use of NSAIDs (other than low-dose aspirin) by elderly patients could double the risk of being admitted to hospital with an episode of CHF, and the risk of heart failure increased in NSAIDs users who had a history of heart disease [34]. Usually, elderly patients given NSAIDs have to consider some risk factors. They need intensive monitoring and patient education is important. Also, urine analysis should be done, dehydration, diuretic therapy, cirrhosis, and underlying renal disease should all be screened. Serum potassium levels should be monitored, particularly in patients on other potassium-sparing drugs. Other drugs that the patient is taking must be considered so that adverse interactions can be avoided. Therefore, any unusual sign or symptom in a patient on NSAIDs should prompt a thorough review of medications and systems to ensure that the NSAIDs are not directly or indirectly responsible for these symptoms and signs [35].

Risk of myocardial infarction

Using NSAIDs by outpatients with stable atherothrombotic disease was found to be associated with a higher risk of myocardial infarction, stroke, and hospitalizations for both ischemia and heart failure [36].

Many studies found that there is a relation between increasing NSAIDs in daily dose and risk of acute myocardial infarction [37]. A meta-analysis study found that all NSAIDs categories, including naproxen were significantly increasing the risk of acute myocardial infarction. The greater risks were associated with rofecoxib in contrast with other NSAIDs [37]. Another study found that ketorolac, a selective COX-2 inhibitor, was associated with the highest risk of AMI compared to etoricoxib, rofecoxib, and celecoxib, which were associated with a small increase in the risk of AMI [38].

The risk of myocardial infarction was elevated regardless of the duration of therapy [9]. In contrast, other studies have shown that a longer duration of NSAIDs use generally does not seem to be associated with greater probabilities of increased risk of myocardial infarction. The risk was greater during the first month of NSAIDs using higher doses [37]. Even though using aspirin as a cardioprotective agent, aspirin does not appear to decrease the risk of acute MI for any of the common NSAIDs (Celecoxib, Rofecoxib, Diclofenac, Ibuprofen or Naproxen) [39]. Other parameters such as age and gender did not modify the risk of myocardial infarction in any NSAIDs category [9].

A study done on patients with spondyloarthritis and osteoarthritis who were using NSAIDs has found that the current use of diclofenac in spondyloarthritis was associated with two-fold to three-fold higher risk of MI relative to remote use of any NSAIDs [40].

Risk of blood pressure elevation

Hypertension is one of the major contributors to developing CVDs. Hypertension may cause left ventricular hypertrophy, systolic and diastolic dysfunction leading to arrhythmias and heart failure [41]. All NSAIDs, except for aspirin, could potentially increase blood pressure when taken at necessary doses to alleviate pain and inflammation in both hypertensive and normotensive individuals [42].

NSAIDs can inhibit renal prostaglandin through their ability to block COX enzymes [43]. They lead to an increase in sodium retention and to excess water retention by inhibiting the natriuretic effect of COX-2; water retention can also occur by the inhibition of renal vasodilating prostaglandins, leading to an increase in the total blood volume and causing altered systolic and diastolic blood pressure

[43,44]. Also, NSAIDs can reduce the efficacy of antihypertensive medications to varying degrees. Besides, calcium channel blockers are least likely to be affected by NSAIDs [45,46]. Practically, all COX-2 inhibitors have been associated with increased blood pressure or impaired response to antihypertensive drugs [47]. In a study, researchers found that chronic NSAIDs use for nearly 3 years was related to slight lowering of blood pressure levels compared with nonuse [48].

Hypertensive patients who are newly initiated with NSAIDs experience an immediate clinically relevant effect on systolic blood pressure (SBP). SBP should be monitored before and after initiation of NSAIDs, especially in patients prescribed high dosages of NSAIDs [49].

Studies conducted to compare the effect of different NSAIDs on blood pressure have found that the average systolic blood pressure of patients on angiotensin-converting enzyme inhibitors (ACE-Is) or calcium channel blocker (CCBs) was increased by 3 mmHg, and by 6 mmHg in patients who were using beta-adrenergic blockers. NSAIDs have shown no effect on blood pressure in patients who are on diuretics, and patients on combinations of two or more antihypertensive medications [50]. The risk of a rise in SBP increased in patients using etoricoxib, and patients using more than one defined daily dose [49].

Incidences of myocardial infarction, stroke, and cardiovascular mortality may increase in hypertensive individuals who chronically use NSAIDs in comparison to nonchronic NSAID users [48].

Risk of developing heart failure

Use of traditional NSAIDs and Coxibs can lead to the development of congestive heart failure in susceptible individuals [51]. A large meta-analysis of over 600 individuals have found that the risk of hospitalization due to heart failure was roughly doubled by all NSAID regimens studied (Coxib, Diclofenac, Ibuprofen, Naproxen) [52].

A study found that current users of any NSAID had a 24% higher risk of heart failure than past users. Additionally, there was a significantly higher risk of heart failure in association with current use of nine individual NSAIDs than with past use of any NSAIDs (Ketorolac, Etoricoxib, Indomethacin, Rofecoxib, Piroxicam, Diclofenac, Ibuprofen, Nimesulide, and Naproxen). Other less frequently used NSAIDs were also found to be associated with an increased risk of heart failure (e.g. Sulindac, Acemethacin, and Dexibuprofen). Additionally, the increase in the risk of heart failure affected both patients with and without prior heart failure (for all NSAIDs). However, patients without prior heart failure are less susceptible to heart failure decompensations. In addition, indomethacin and etoricoxib seemed to increase the risk of hospital admission from heart failure even if they were used at medium doses [53]. These findings support the hypothesis that selective and non-selective COX 2 inhibitors may increase the risk of heart failure. However, the magnitude of this effect varies among individual drugs and according to the dose used [54]. The effect of individual NSAIDs can depend on a complex interaction of pharmacological properties, including duration and extent of platelet inhibition, the extent of blood pressure increase, and properties possibly unique to the molecule [55].

Exposure to NSAID in patients who were admitted with a primary diagnosis of heart failure was low by 3.9%. Also, they were associated with adverse outcomes including longer duration of stay and higher prevalence or worsening of renal function [56]. Another study has found that 19% of hospital admissions with CHF were caused by NSAIDs, and it was positively related to the dose of NSAID consumed in the previous week and was greater with long half-life than with short half-life drugs [34].

Current guidelines limit the use of NSAIDs in patients predisposed to heart failure, with a full contraindication for patients with diagnosed heart failure [57].

Risk of atrial fibrillation

Atrial fibrillation is the most common rhythm disorder observed in clinical practice. Its prevalence more than doubles during each advancing decade of life, from 0.5% at age 50-59 years to above 10% at age 80-89 years [58]. It is associated with the increase in the mortality and morbidity, mainly due to hemodynamic impairments that exacerbate or even cause heart failure [59] and a 3-fold to 4-fold increase in the risk of thromboembolic stroke [60].

Multiple studies indicate an elevated risk of atrial fibrillation (AF) associated with the use of NSAIDs [61-64]. A meta-analysis study found that NSAIDs increase the risk of developing AF by 12%, and it was greater among the new user with a 53% increase in the risk [65]. Also, another study conducted on patients aged 40-89 years revealed an association between the current use of NSAIDs and the development of AF and has found that both non-selective NSAIDs and COX-2 inhibitors were associated with increasing the risk of chronic AF. Patients who took NSAIDs for more than one year were at a higher risk [66]. NSAID use had an elevated risk of AF compared to non-users, and those who used non-selective NSAIDs had a higher risk of AF compared to selective NSAIDs [67]. Similarly, a larger cohort study found that new NSAIDs use may predispose patients to AF, and those with heart failure almost had a doubled risk. Also, the use of selective COX2 inhibitors was not significantly related to AF occurrence, except in patients with chronic kidney or pulmonary disease [62]. The risk of AF associated with NSAIDs among patients with prior myocardial infarction (MI) was found to be increased regardless of the type of NSAID or with short-term (0 - 14 days) treatment, also NSAID users were associated with a poorer prognosis [68]. Instead, to increase the risk of developing AF, NSAIDs can also cause comorbidities in a patient with AF. NSAIDs were found to be associated with increased absolute risks for serious bleeding and thromboembolism across all antithrombotic regimens [69].

In contrast, there are studies found that NSAIDs use could be a benefit in AF after coronary artery bypass grafting (CABG) surgery. A study found that NSAIDs given in the immediate postoperative period of CABG surgery are relatively safe and effective in reducing the incidence of AF [70]. Another study found that postoperative use of naproxen decreased the duration of AF duration, but not its incidence. The study also found that naproxen was associated with a significant increase in the incidence of new-onset postoperative renal failure that is why their findings do not support the routine use of naproxen as prophylaxis for preventing atrial fibrillation in patients undergoing isolated CABG surgery [61].

Conclusion

NSAIDs can cause a lot of cardiovascular adverse events as heart failure, myocardial infarction, congestive heart failure, hypertension, atrial fibrillation, and can even lead to death. Therefore, NSAIDs should be used at the lowest effective dose for the shortest possible duration of therapy especially in the elderly and patients at high risk for an adverse event.

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