

Nonsteroidal Anti-inflammatory Drugs: Cardiovascular, Cerebrovascular and Renal Effects

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Abstract

The nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most often prescribed drugs in the world. This heterogeneous class of drugs includes aspirin and several other selective or non-selective cyclooxygenase (COX) inhibitors. The non-selective NSAIDs are the oldest ones and are called traditional or conventional NSAIDs. The selective NSAIDs are called COX-2 inhibitors. In recent years, the safety of NSAID use in clinical practice has been questioned, especially that of the selective COX-2 inhibitors. The evidence on the increase in cardiovascular risk with the use of NSAIDs is still scarce, due to the lack of randomized and controlled studies with the capacity of evaluating relevant cardiovascular outcomes. However, the results of prospective clinical trials and meta-analyses indicate that the selective COX-2 inhibitors present important adverse cardiovascular effects, which include increased risk of myocardial infarction, cerebrovascular accident, heart failure, kidney failure and arterial hypertension. The risk of these adverse effects is higher among patients with a previous history of cardiovascular disease or those at high risk to develop it. In these patients, the use of COX-2 inhibitors must be limited to those for which there is no appropriate alternative and, even in these cases, only at low doses and for as little time as possible.

Although the most frequent adverse effects have been related to the selective COX-2 inhibition, the absence of selectiveness for this isoenzyme does not completely eliminate the risk of cardiovascular events; therefore, all drugs belonging to the large spectrum of NSAIDs should only be prescribed after consideration of the risk/benefit balance.

Introduction

The nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most often prescribed drugs in the world. They are used mainly in the treatment of inflammation, pain and

Key words

Anti-inflammatory agents, non-steroidal/adverse effects; risk; physiological effects of drugs/heart/kidney/cerebrum.

edema, as well as of osteoarthritis, rheumatoid arthritis and musculoskeletal disorders. This heterogeneous class of drugs includes aspirin and several other selective or non-selective cyclooxygenase (COX) inhibitors (Table 1). Aspirin is the oldest and more extensively studied NSAID; however, it is considered separately from the others, due to its predominant use in the treatment of cardiovascular and cerebrovascular diseases at low doses¹.

The non-selective NSAIDs are the oldest ones and are called traditional or conventional NSAIDs. The selective NSAIDs are called COX-2 inhibitors². In recent years, the safety of NSAID use in clinical practice has been questioned, especially that of the selective COX-2 inhibitors in the presence of certain conditions and diseases, which has led to the removal of some of these drugs from the market.

The traditional NSAIDs can present a pattern of COX-2 selectiveness similar to that of COX-2 inhibitors, such as diclofenac when compared to celecoxib, or they can be more active COX-1 inhibitors, such as naproxen and ibuprofen.

Physiopathology

The phospholipase A2 enzyme activation, in response to several stimuli, hydrolyzes the phospholipids of the membrane, releasing arachidonic acid in the cytoplasm. The latter functions as substrate for two enzyme pathways: the

Table 1 - Nonsteroidal anti-inflammatory drugs according to their cyclooxygenase selectiveness

Nonsteroidal anti-inflammatory drugs Classification	
Non-selective (COX-1 and 2) (traditional, conventional)	Selectives (COX-2) COXIBs
Aspirin	Rofecoxib
Acetaminophen	Valdecoxib
Indomethacin (Indocin)	Parecoxib
Ibuprofen (Advil, Motrin)	Celecoxib
Naproxen (Aleve, Naprosyn)	Etoricoxib
Sulindac (Clinoril)	Lumiracoxib
Diclofenac (Voltaren, Cataflam)	
Piroxicam (Feldene)	
β- Piroxicam (Cycladol)	
Meloxicam (Movatec)	
Ketoprofen (Profenid)	

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cyclooxygenase and the lipoxygenase. Prostaglandin (PG) H_2 is generated through the COX pathway, which stimulates the formation of several prostanoids, including several prostaglandins - PGI_2 , PGD_2 , PGE_2 , $PGF_2\alpha$ -, and thromboxane A_2 . Leukotrienes, lipoxins and other products are formed through the lipoxygenase pathway.

In 1991, the existence of two isoforms of the cyclooxygenase enzyme were demonstrated; they were called COX-1 and COX-2 and were found to be codified by different genes, with similar chemical structures, 60% of homology in the amino acid sequence and singular patterns of expression¹⁻³. The COX-1 isoform is expressed in a *constitutive* (constant) way in most tissues, whereas COX-2 is *induced* in inflammations. COX-1 is essential for the maintenance of the normal physiological state of many tissues, including the protection of the gastrointestinal mucosa, control of renal blood flow, homeostasis, autoimmune responses, pulmonary, central nervous system, cardiovascular and reproductive functions³⁻⁵. COX-2, induced in inflammation by several stimuli - such as cytokines, endotoxins and growth factors -, originates inducing prostaglandins, which contribute to the development of edema, rubor, fever and hyperalgesia. COX-2 is also expressed in normal endothelial vascular cells, which secrete prostacyclin in response to shearing stress. The COX-2 blocking results in prostacyclin synthesis inhibition⁶⁻⁸.

The COX enzymes have an important role in cardiovascular homeostasis. The thromboxane A_2 (TXA_2), synthesized mainly in the platelets by the COX-1 activity, causes platelet aggregation, vasoconstriction and proliferation of smooth muscle cells. On the other hand, the synthesis of prostacyclin, broadly mediated by the activity of COX-2 in macrovascular endothelial cells, contrasts with these effects. The prostacyclin is the main prostanoid

secreted by the endothelial cells. It causes relaxation of the vascular smooth muscle cells and is a potent vasodilator. Additionally, as it acts on the IP receptors of platelets, it has an important anti-platelet activity⁹. Several prostanoids, especially prostacyclin and PGE_2 , are crucial to protect the gastric mucosa from the erosive effects of stomach acid, as well as to maintain the naturally healthy condition of the gastric mucosa. These prostaglandins are produced by the action of the COX-1⁹ (Figure 1). The consequences of the COX-1 blocking in the gastrointestinal tract are the inhibition of the mucosa protection and increased acid secretion, which can lead to erosion, ulceration, perforation and hemorrhage. The likelihood of ulcers or bleeding increases with high-dose or prolonged use of NSAIDs, concomitant administration of corticosteroids and/or anticoagulants, smoking, alcohol consumption and advanced age.

On the other hand, the selective inhibition of COX-2 can induce the relative decrease of endothelial production of prostacyclin, whereas the platelet production of TXA_2 is not altered. This imbalance of hemostatic prostanoids can increase the risk of thrombosis and vascular events. It was also demonstrated, in non-anesthetized mice, that COX-2 mediates cardioprotective effects during the late phase of myocardial pre-conditioning¹⁰. However, the administration of COX-2 inhibitors to the animals, 24 hours after the ischemic pre-conditioning, eliminates this cardioprotective effect against the "stunned" myocardium and myocardial infarction. These subsequent studies indicated that the up-regulation of COX-2 has a key-role in cardioprotection mediated by PGE_2 and PGI_2 ¹⁰⁻¹².

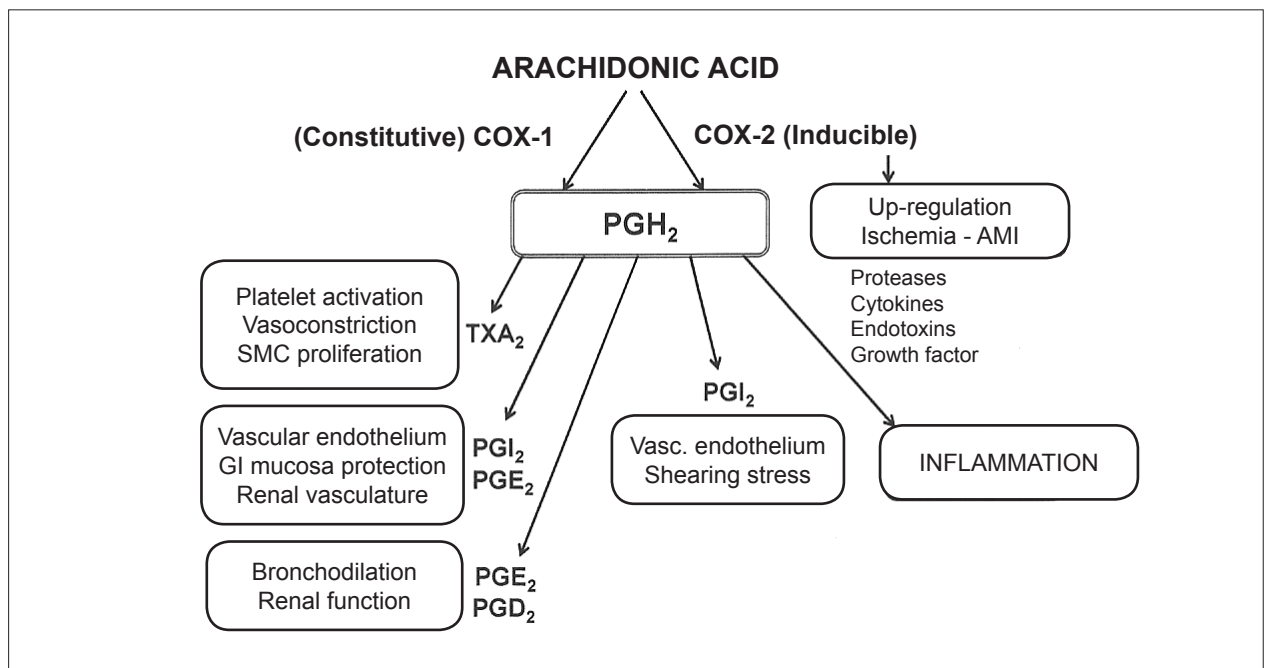


Figure 1 - Schematic representation of the effects related to the COX-1 and COX-2 activation. COX - cyclooxygenase; PG - prostaglandin; TX - thromboxane; AMI - acute myocardial infarction.

Pharmacology

The differences in the biological effects of COX inhibitors result from the degree of selectiveness for the two isoenzymes, the specific tissue variations in its distribution and the enzymes that convert PGH_2 into specific prostanoids.

The COX non-selective NSAIDs inhibit the production of prostaglandins in the gastrointestinal mucosa and can cause gastroduodenitis, gastric ulcer and digestive bleeding. These NSAIDs, similarly to aspirin, reduce the platelet production of TXA_2 due to the COX-1 blocking and prevent arterial thrombosis (Figure 2). Recently, it has been postulated that the COX-2 selective inhibitors increase the cardiovascular risk. These agents do not block the formation of TXA_2 or have anti-platelet action, due to the minimal inhibition of COX-1, but they decrease prostacyclin production¹². The increase in cardiovascular risk could result from the lack of opposition to the action of TXA_2 and the propensity to thrombosis. Additionally, several experimental models have shown the cardioprotective effect of COX-2, which could be blocked by the inhibitors of this isoform. COX-2 is expressed at low levels by the endothelial cells in static conditions; however, it is induced by shearing stress⁸. These findings suggest that the decrease in prostacyclin production, secondary to the decrease in COX-2, can increase the risk of focal atherogenesis in vascular bifurcation sites.

From the 1960s on, many non-selective NSAIDs were introduced in clinical practice. These traditional or conventional NSAIDs present varied inhibitory effects in relation to COX-1 and COX-2, as well as the side effects in the digestive tube. The aspirin is approximately 166 times more potent as COX-1 inhibitor in relation to COX-2¹³. The aspirin acetylates and irreversibly inhibits the COX-1 isoenzyme, which leads to complete platelet inhibition, during the platelet

life-time¹⁴. Other non-selective NSAIDs, such as naproxen, ibuprofen and piroxicam, cause variable inhibition of COX-1 and COX-2 and result in reversible platelet inhibition.

Cardiovascular effects

Due to the relatively scarce expression of COX-2 in the gastrointestinal tract and its high expression in inflammatory and/or painful tissues, selective COX-2 inhibitors were developed and introduced in therapeutics from 1999 on, with the objective of minimizing gastrointestinal toxicity of non-selective NSAIDs¹⁵. The selective COX-2 inhibitors are as or more effective than the non-selective NSAIDs for the treatment of inflammation and associated symptoms. However, as the platelets primarily express COX-1, these drugs do not have anti-thrombotic properties. Based on animal studies, observation of records and clinical trials, it has been proposed that the most important consequences of the selective inhibition of COX-2 in relation to the heart are the propensity to thrombosis, through the shift in the pro-thrombotic/anti-thrombotic balance on the endothelial surface and the loss of the protective effect of the up-regulation of COX-2 in myocardial ischemia and myocardial infarction¹⁵⁻¹⁷ (Figure 3).

Renal effects

Homeostatic prostaglandins - prostacyclin, -PGE_2 and PGD_2 -, generated through the action of COX-1 in distinct regions of the kidneys, dilate the vasculature, decrease the renal vascular resistance and increase the organ perfusion. This leads to the redistribution of the blood flow from the renal cortex to the nephrons in the intramedullary region^{18,19}. The inhibition of these mechanisms tend to decrease the total renal perfusion

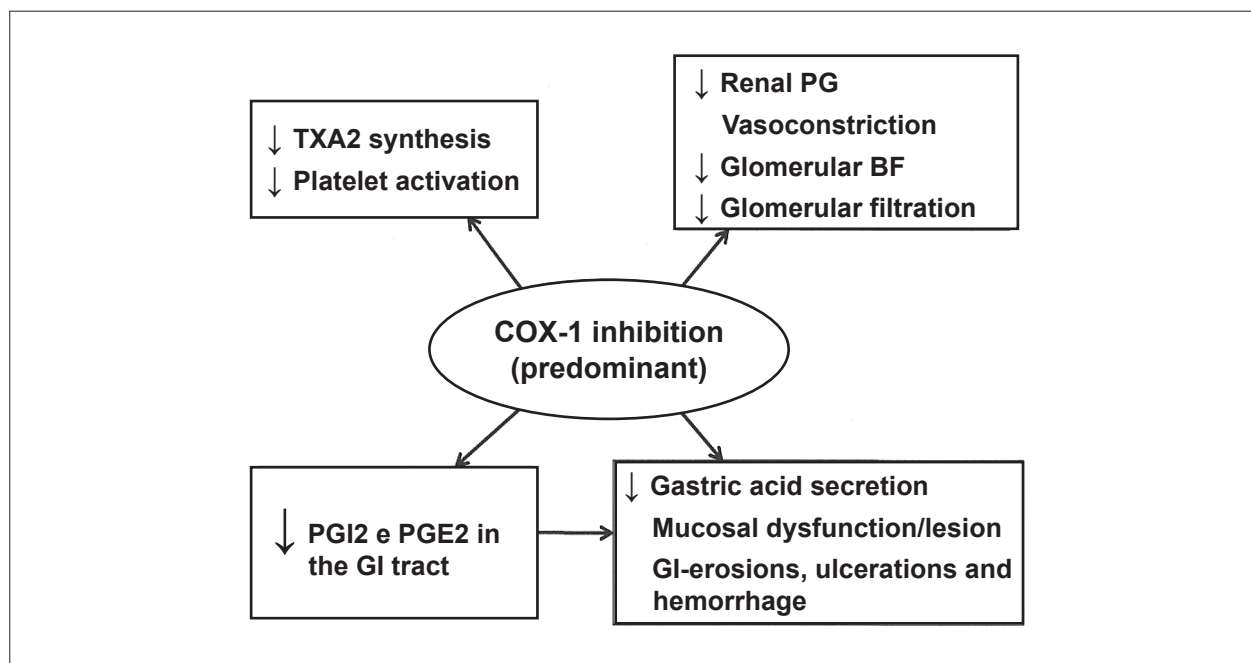


Figure 2 - Representation of the effects related to the COX-1 inhibition. COX - cyclooxygenase; PG - prostaglandin; TX - thromboxane; GI - gastrointestinal.

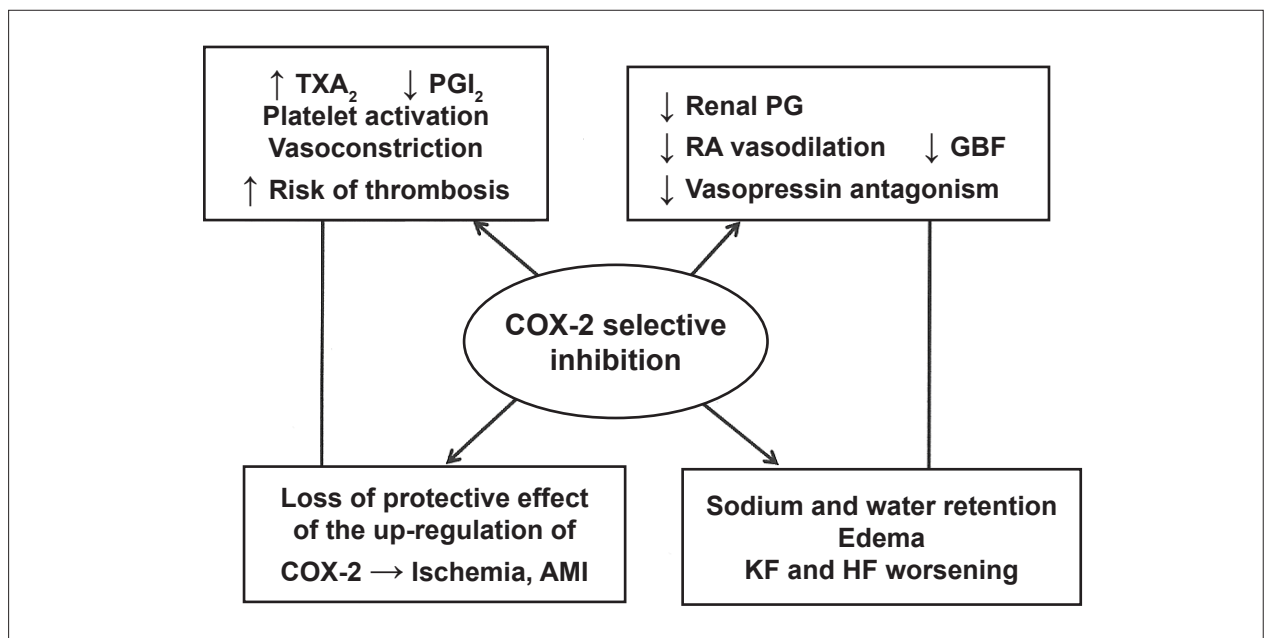


Figure 3 - Schematic representation of the effects related to the COX-2 inhibition. COX - cyclooxygenase; PG - prostaglandin; TX - thromboxane; GI - gastrointestinal; RA - renal arteriole; GBF - glomerular blood flow; AMI - acute myocardial infarction; HF - heart failure; KF - kidney failure.

and redistribute the blood flow to the cortex, a process that culminates in acute renal vasoconstriction, medullary ischemia and, under certain conditions, acute renal failure.

Additionally, PGE₂ and PGF₂α mediate the diuretic and natriuretic effects, whereas PGE₂ and PGI₂ antagonize the action of vasopressin. Both, generated at the glomeruli, contribute to maintain the glomerular filtration rate. These prostaglandins constitute a self-regulating mechanism in the presence of renal perfusion decrease, as in heart failure and hypovolemia conditions.

The responses to the decreased renal blood flow and renal hemodynamic alterations include the stimulation of the renin-angiotensin-aldosterone system, which results in vasoconstriction and sodium and water retention, as well as the stimulation of the sympathetic nervous system, promoting a further increase in vascular tonus.

In these situations, the prostaglandins promote compensatory dilation of the renal vasculature to guarantee a normal blood flow and prevent the acute functional deterioration of the kidney. Additionally, these prostaglandins reduce the release of noradrenaline, which also favors vasodilation. It is mostly through the attenuation of these contra-regulatory mechanisms mediated by prostaglandins that NSAIDs impair the renal function, especially in high-risk patients, who already present a decrease in renal perfusion (Figure 4).

Sodium and water retention and edema are adverse effects of NSAIDs, but they are usually mild and sub-clinical^{18,20}. The prevalence of symptomatic edema is 3% to 5%²¹. Another potentially adverse reaction induced by NSAIDs is hyperkalemia. The NSAIDs attenuate the release of renin mediated by prostaglandins, reduce the formation of aldosterone and, as a consequence, decrease

the excretion of potassium. Additionally, in the presence of a decreased glomerular flow, the opposition to the natriuretic and diuretic effects of the prostaglandins by the NSAIDs can increase the sodium and water resorption in the renal tubule, with a decrease in the Na⁺-K⁺ exchange in the distal néphron²². The patients that are more susceptible to develop hyperkalemia are those that use simultaneously potassium supplement, potassium-sparing diuretics and/or angiotensin-converting enzyme inhibitor (ACEI), in addition to those with basal renal dysfunction, heart failure or diabetes mellitus²¹.

The renal complications induced by NSAIDs are reversible with the suppression of these drugs. However, in the presence of associated adverse conditions, they can, albeit rarely, cause acute renal dysfunction, nephrotic syndrome, interstitial nephritis or renal papillary necrosis.

The prolonged use of NSAIDs can cause an increase of 5 to 6 mmHg in the mean blood pressure, especially in hypertensive individuals and can interfere with the anti-hypertensive effects of diuretics, beta-blockers and ACE inhibitors. However, there is a large variation concerning the results among the drugs and among the clinical trials.

Clinical trials

Some clinical and experimental trials have suggested a probable association between COX-2 inhibitors and the increase in cardiovascular risk. To date, no complete prospective trial has evaluated this problem. However, clinical trials designed to assess gastrointestinal outcomes have reported cardiovascular events. The outcomes of these clinical trials, which used different COX-2 inhibitors, were inconsistent and it is likely that the patient's basal risk has an important role.

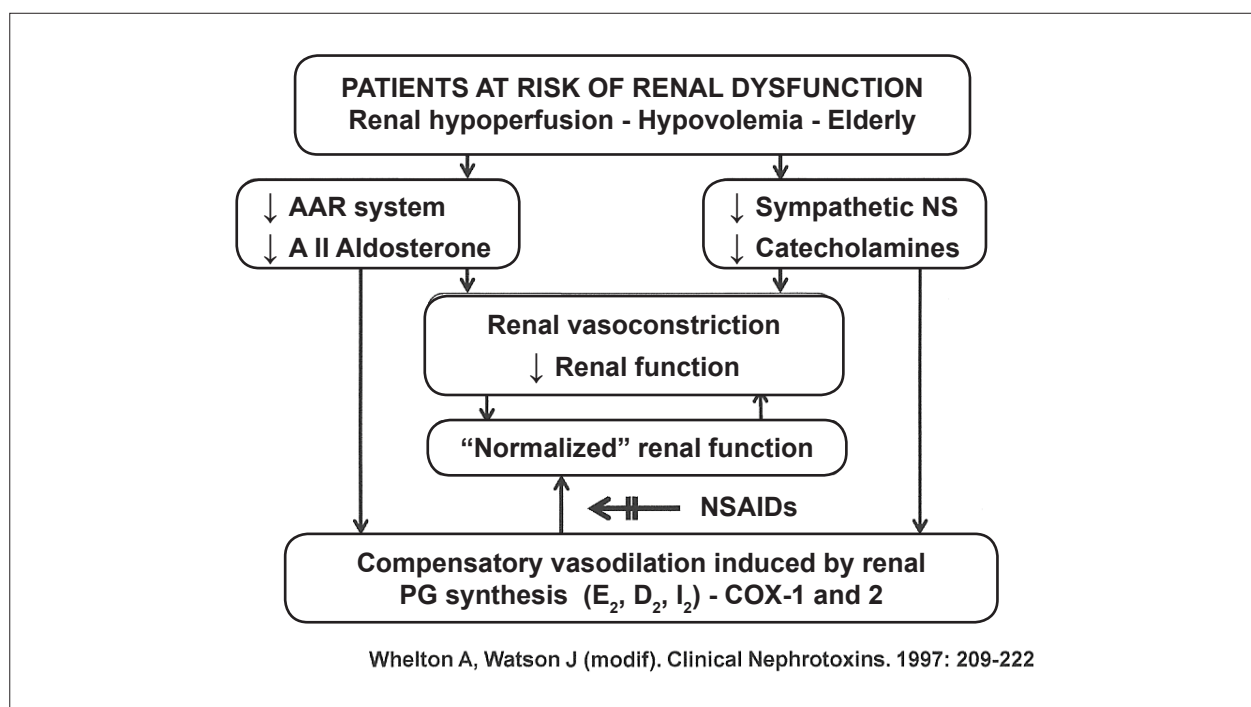


Figure 4 - Schematic representation of the effects of NSAIDs in the blocking of compensatory actions induced by prostaglandins in the presence of kidney dysfunction. All - angiotensin II; PG - prostaglandin; RAA - renin-angiotensin-aldosterone; Arrow = inhibition.

Cardiovascular events

The first studies evaluated the rofecoxib, which has been removed from the market. The Vioxx Gastrointestinal Outcome Research Study (VIGOR)²³ compared rofecoxib, 50 mg/day with naproxen, 500 mg 2x day, in 8,076 patients with rheumatoid arthritis. Patients with recent cardiovascular events or those using aspirin were excluded. The primary outcome was upper gastrointestinal event. Although it was not the objective of the study, a higher incidence of myocardial infarction was observed with rofecoxib (0.4%/year), when compared to naproxen (0.1%/year). Gastrointestinal bleeding was significantly lower with rofecoxib, when compared with naproxen (RR (relative risk) = 0.4). Naproxen is a strong inhibitor of COX-1 and also inhibits COX-2 by 71%, while diclofenac inhibits this isoenzyme by 94%²⁴.

The Multinational Etoricoxib and Diclofenac Arthritis Long-Term MEDAL Study Program²⁵ compared the agent that was highly selective for COX-2 inhibition (Etoricoxib) with a traditional NSAID, diclofenac, relatively less selective for COX-2 inhibition. This study did not show inferiority of the Etoricoxib when compared to diclofenac, regarding the thrombotic cardiovascular events.

Although the VIGOR²³ study reported an increase in the myocardial infarction rate among the patients allocated to rofecoxib, when compared to those allocated to naproxen, (4 vs 1; p < 0.001), this difference might have occurred in part due to the inhibitory effect of the platelet aggregation of naproxen in the posology scheme used in the study. However, the outcomes of the APPROVE - The Adenomatous Polyp Prevention on VIOXX²⁴ - study,

the first large study that compared a selective inhibitor of COX-2 with a placebo, showed a two-fold increase in cardiovascular events with rofecoxib. Soon after, the APC⁵ study, which compared celecoxib with a placebo, reported a similar incidence of vascular events with this selective NSAID²⁶. However, the Celecoxib Long-Term Arthritis Safety Study (CLASS)²⁷, which included 8,059 patients with osteoarthritis or rheumatoid arthritis treated with celecoxib, 400 mg 2x day, or another non-selective COX inhibitor com (ibuprofen 800 mg, 3x day, or diclofenac, 75 mg 2x day), did not show any statistically significant difference regarding the incidence of cardiovascular events between the groups. The rates of bleeding were higher with ibuprofen and diclofenac (6.0%) in comparison with celecoxib (3.1%). It must be stated that diclofenac and ibuprofen have a relatively weak anti-platelet activity.

In 2006, Kearney et al²⁸ published the results of the meta-analysis of 138 randomized studies involving traditional NSAIDs and selective COX-2 inhibitors, comparing them with a placebo and with each other. The primary outcome was severe vascular event, defined as myocardial infarction, cerebrovascular accident, or vascular death. Overall, in 121 placebo-controlled studies, there were 216 vascular events among 18,190 patients/year treated with selective COX-2 inhibitors (1.2%/year), compared with 112 studies in 12,639 patients/year in the placebo group (0.9%/year), corresponding to a relative 42% increase in the incidence of a first severe vascular event (rate ratio 1.42; p = 0.003), without significant heterogeneity among the different selective COX-2 inhibitors.

This outcome was mainly attributable to the increased risk of myocardial infarction (0.6%/yr vs 0.33%/yr; rate ratio 1.86; $p = 0.0003$), with a small difference in the other vascular outcomes. Around two-thirds of the vascular events occurred among the nine long-term studies (one year or more of planned treatment, mean of 139 weeks). In these studies, the use of selective COX-2 inhibitor was associated to a 45% increase in the incidence of vascular events (rate ratio 1.45; $p = 0.005$), without significant heterogeneity between the rate ratio of events. Overall, the incidence of severe vascular events was similar between a selective COX-2 inhibitor and any traditional NSAID (1.0%/yr vs 0.9%/yr). However, a marked heterogeneity was observed among the studies that compared a selective COX-2 inhibitor with naproxen: vascular events (rate ratio 1.57; $p = 0.0006$); myocardial infarction ($p = 0.04$); cerebrovascular accident (CVA) ($p = 0.06$); vascular death ($p = 0.02$).

The summarization of the rate ratio of vascular events in comparison to placebo was 0.92 for naproxen, 1.51 for ibuprofen and 1.63 for diclofenac. In conclusion, the selective COX-2 inhibitors were associated with a moderate increase in the risk of vascular events; the same occurred with the non-selective NSAIDs ibuprofen and diclofenac at high doses, but not with naproxen. Regarding the association of a NSAID with aspirin, the evidence indicates that ibuprofen, but not acetaminophen, diclofenac or rofecoxib interfere with the capacity of aspirin to irreversibly acetylate the platelet COX-1 enzyme. This could reduce the protective effect of aspirin against atherothrombotic events.

Recently, Garcia Rodriguez et al²⁹ evaluated the association between the frequency, dose and duration of use of different NSAIDs and the risk of myocardial infarction in the general population, in a retrospective cohort study. They also verified whether the degree of COX-2 inhibition in whole blood could be a "surrogate" biochemical predictor for the risk of myocardial infarction associated with NSAIDs. A total of 8,852 cases of non-fatal infarction were identified in patients aged 50 to 80 years, between 2000 and 2005 and the case-control analysis was performed. The risk of infarction was correlated with the degree of platelet COX-1 inhibition and monocyte COX-2 *in vitro* through the mean therapeutic concentration of each NSAID.

The risk of myocardial infarction increased with the regular use of NSAIDs (RR 1.35; confidence interval - CI 1.23 to 1.48) and this risk was correlated with the posology and duration of treatment. The group of NSAIDs with a degree of COX-2 inhibition < 90% - ibuprofen, meloxicam, celecoxib and etoricoxib - presented a RR of 1.18 (CI 1.02 to 1.28), whereas the group of NSAIDs with higher COX-2 inhibition - rofecoxib, indomethacin, diclofenac and piroxicam -, presented RR = 1.60 (CI 1.41 to 1.81; $p < 0.01$ for interaction). The degree of COX-1 and COX-2 activity inhibition in whole blood, *in vitro*, induced by the NSAIDs individually, showed that, except for naproxen and ibuprofen, all the others inhibited COX-2 more intensely than COX-1 at therapeutic concentrations. The authors concluded that the magnitude of the inhibition of COX-2-dependent prostacyclin can represent the main factor for the increased risk of myocardial infarction among NSAIDs, with non-functional suppression of COX-1. This

property is shared by most traditional NSAIDs and COX-2 inhibitors and the measurement of the concentration of COX-2 in whole blood can represent a surrogate outcome to predict the cardiovascular risk of these drugs. The division of NSAIDs in selective and non-selective COX-2 inhibitors represents only partially the prediction of cardiovascular risk of NSAIDs. These results are consistent with those from case-control studies and randomized clinical trials^{28,30}, however, only partially, with the current view that the selectiveness for COX-2 is a necessary attribute for cardiovascular risk. In fact, it was demonstrated that the prolonged action and high doses of the active compound are associated with an increased risk for any NSAID. These findings suggest that the degree of COX inhibition by therapeutic levels of NSAIDs must be considered the major determinant factor of cardiovascular risk^{5,31,32}. Considering that the vasculature and COX-2 are the most important sources and the catalyzers of PGI₂⁵, the authors inferred that only the intense reduction in COX-2 activity ($\geq 95\%$) results in a significant decrease in the synthesis of PGI₂ *in vivo*, and, eventually, in the increased risk of myocardial infarction²⁹. Therefore, an increase in the cardiovascular risk seems to be clearly associated to the effective inhibition of COX-2, unless it is attenuated by the concomitant effective inhibition of platelet COX-1.

Arterial hypertension

Two large meta-analyses^{33,34}, encompassing more than 90 clinical trials, demonstrated that the NSAIDs can elevate the blood pressure (BP). Both showed a higher elevation in hypertensive patients. The analysis by Pope et al³³ showed that indomethacin and naproxen increased the mean blood pressure by 3.59 mmHg and 3.74 mmHg, respectively. Piroxicam resulted in a negligible mean BP increase (0.49 mmHg). The increase in BP caused by NSAIDs was associated with the significant decline in the concentrations of prostaglandins and renin.

In the meta-analysis by Jonhson et al³⁴, the data showed that the NSAIDs increased the mean supine BP by around 5.0 mmHg. O Piroxicam induced o the highest increase (6.2 mmHg). Aspirin, sulindac and flurbiprofen presented the lowest increase in BP; indomethacin and ibuprofen had intermediate effects.

The set of data also showed that the NSAIDs interfere with the anti-hypertensive effects of several classes of these agents, especially those of which mechanism of action also involves the synthesis of vasodilating prostaglandins, such as diuretics, angiotensin-converting enzyme inhibitor and beta-blockers. Calcium-channel blockers and angiotensin-II receptor antagonists showed less interference by NSAIDs on their effects^{18,35}.

Cerebrovascular events

In clinical trials, the use of selective COX-2 inhibitor NSAIDs was associated with an increased risk of cardiovascular events and death³⁶. Most post hoc analyses of the trials showed the combined cardiovascular and cerebrovascular events as the clinical outcome, without any other specification of cardiovascular risk³⁶. The meta-analysis by Kearney et al²⁸ did

not show any difference in the incidence of cerebrovascular events with NSAIDs.

Recently, Haag et al³⁷ evaluated 7,636 individuals with a mean age of 70.2 years, of which 61.3% were women, with no manifestations of previous brain ischemia (1991-1993), regarding the incidence of cerebrovascular accident (CVA) up to September 2004. Of 70,063 individuals/year of follow-up (mean = 9.2 years), 807 individuals developed CVA (460 ischemic, 74 hemorrhagic and 273 not specified). The regular users of non-selective NSAIDs (HR 1.72; 95% CI: 1.22 to 2.44) and selective COX-2 inhibitors (HR 2.75; 95% CI: 1.28 to 5.95) presented a higher risk of stroke; however, the same was not true for those that took selective COX-1 inhibitors (HR 1.1; 95% CI: 0.41 to 2.97). The hazard ratio for ischemic stroke was 1.68 (1.05 to 2.69) for non-selective agents and 4.54 (2.06 to 9.98) for selective agents. Considered separately, the current use of naproxen (non-selective) was associated with a HR of 2.63 (95% CI: 1.47 to 4.72) and the use of rofecoxib (selective for COX-2) to a higher risk of stroke (HR 3.38; 95% CI: 1.48 to 7.74). The hazard ratios for diclofenac (1.60; 1.0 to 2.57), ibuprofen (1.47; 0.73 to 3.00) and celecoxib (3.79; 0.52 to 2.76) were > 1.00, but did not reach statistical significance.

The authors concluded that in the general population, the risk of stroke was higher with the current use of selective NSAIDs, although it was not limited to them, as the event also occurs with the non-selective NSAIDs.

Heart failure

The addition of a NSAID to the therapeutic scheme of a patient undergoing treatment with diuretics to control cardiovascular disease, associated with sodium and water retention, increases the probability of developing heart failure. In a study of 10,000 individuals, aged 55 years or older, the concomitant use of diuretics and NSAIDs was associated with a two-fold increase in the rate of hospitalizations due to heart failure³⁸. Patients with a previous history of congestive heart failure presented a higher risk³⁸.

Gastrointestinal effects

The most important adverse effects of NSAIDs occur in the gastrointestinal system. Approximately 20% of the patients do not tolerate the treatment with NSAIDs due to such effects, including abdominal pain, pyrosis and diarrhea¹⁶. The long-term treatment can cause gastric and duodenal erosions and ulcers. Although many of these patients are asymptomatic, they present a high risk of developing severe complications, such as stomach bleeding and perforation. The annual risk of these severe complications is 1% to 4% during the chronic treatment with NSAIDs. The elderly, women, individuals with rheumatoid arthritis, previous history of gastroduodenal bleeding, those using anti-thrombotic or corticosteroid agents, those using high doses of NSAIDs and those with a severe systemic disease are more prone to present them.

These adverse effects result from the blocking of COX-1 in the gastrointestinal mucosa and the consequent inhibition in the production of prostacyclin, PGE₂ and PGD₂ in the stomach.³⁹ These prostaglandins act as cytoprotective agents of the gastrointestinal mucosa; they inhibit the acid secretion by the stomach, increase the local blood flow and the secretion of the protective mucus. Patients with gastroduodenitis, ulcer and mainly digestive bleeding must take proton-pump inhibitors (omeprazole, pantoprazole, lansoprazole etc) daily and the NSAIDs must be taken after the meals⁴⁰.

Conclusions

The evidence on the increased cardiovascular risk with the use of NSAIDs, especially the selective COX-2 inhibitors, is still incomplete, mainly due to the lack of randomized and controlled trials with the power to evaluate relevant cardiovascular outcomes. As the differences among the several NSAIDs are probably small, large comparative clinical trials are necessary to identify which anti-inflammatory scheme minimizes the total load of cardiovascular and gastrointestinal adverse events. However, the results of the clinical trials and meta-analyses indicate that the selective COX-2 inhibitors have important adverse cardiovascular effects that include increased risk of myocardial infarction, cerebrovascular accident, heart failure, kidney failure and arterial hypertension. The risk of these adverse events is higher in patients with a previous history of cardiovascular disease or those presenting high risk of developing it. In these patients, the use of COX-2 inhibitors must be limited to those for whom there is no appropriate alternative and even so, only at low doses and for as little time as necessary.

Additionally, more data are necessary on the cardiovascular safety of traditional NSAIDs⁹. Although the most frequent adverse effects have been associated with the selective inhibition of COX-2, the absence of selectiveness for this isoenzyme does not completely rule out the risk of cardiovascular events, so that all drugs belonging to the large spectrum of NSAIDs must only be prescribed after the risk/benefit balance is considered.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

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Study Association

This study is not associated with any post-graduation program.

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