

Selective inhibition of cyclooxygenase-2: risks and benefits

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ABSTRACT

The cyclooxygenase (COX) inhibitors are the most common drugs used worldwide. COX corresponds to an evolutionarily conserved class of enzymes and has two main isoforms: COX-1, which is largely associated with physiological functions, and COX-2, which is largely associated with pathological functions. Their subproducts have an important role in inflammation and pain perception. The COX-2 selective inhibition was designed to minimize gastrointestinal complications of non-selective inhibition. However, this exclusive COX-2 inhibition was associated with serious cardiovascular events, for causing an imbalance between prostacyclin and thromboxane production. The objective of this study is to discuss the mechanisms underlying the cardiovascular effects, pointing out the advantages and disadvantages of the selective or non-selective COX inhibitors.

Keywords: cyclooxygenase 2 inhibitors, cardiovascular diseases, pharmacology.

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INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) represent one of the most diverse classes of drugs clinically available in Brazil. This reflects the continuing need for analgesia in a world population with a high prevalence of chronic pain.¹ In recent data, the anti-inflammatory drugs available in Brazil totaled 66 different compounds: 21 steroidal anti-inflammatory drugs (corticosteroids) and 45 NSAIDs. Of the NSAIDs, 42 correspond to non-selective inhibitors and three to selective inhibitors of cyclooxygenase-2 (COX-2). In addition to these 45, there are also four different associations of compounds.^{2,3}

Although these drugs have diverse chemical structures, they exert their therapeutic effect by their common COX inhibition property. Despite the therapeutic effectiveness, the use of NSAIDs is limited due to their common side effects,

mainly due to gastroduodenal ulcers.^{4,5} In the early 90's, two COX isoforms were clearly identified: COX-1, which appeared to be a constitutive isoform, and COX-2, an inducible form associated with inflammation.

This finding led to the theory that COX-1 inhibition causes unwanted gastrointestinal effects, whereas COX-2 inhibition is responsible for the therapeutic effects.⁶ Considering this new paradigm, there was a great effort from both the pharmaceutical industry and the academic environment to search for selective COX-2 inhibitors. The effort was initially rewarded in 1999 with the launching of the first selective COX-2 inhibitors in the market, celecoxib and rofecoxib. Despite the initial enthusiasm generated by these drugs, the course of history did not show the expected outcome and some of these drugs have been withdrawn from the market, as they cause cardiovascular complications.

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This review aimed to retell this story, in an attempt to reconcile the pharmacology of COX inhibition with different cardiovascular phenotypes observed in human clinical trials.

PROSTANOID SYNTHESIS

Arachidonic acid is an essential fatty acid obtained from the diet, or indirectly, through the conversion of linoleic acid.⁷ This fatty acid is the precursor of a large family of bioactive compounds known as eicosanoids. Due to the biological potency of these compounds, arachidonic acid is maintained at very low levels in the cell through its esterification with membrane phospholipids. Thus, free arachidonic acid availability is described as the limiting step in the production of eicosanoids.⁸ Arachidonic acid is released from the plasma membrane through the action of the phospholipase A₂ enzyme, activating a metabolic cascade that initiates through the action of prostaglandin G/H synthase, commonly called COX.

COX enzymes are highly conserved evolutionarily and there are two forms, COX-1 and COX-2, which are encoded by two different genes.⁹ Both COX-1 and COX-2 form an unstable prostaglandin endoperoxide, PGH₂, from arachidonic acid. PGH₂ is converted by the several enzymes and also by non-enzymatic mechanisms into thromboxane and prostaglandin series D, E, F, and I (Figure 1), which are compounds collectively known as prostanoids. COX is therefore responsible

for the two first steps in the synthesis of prostanoids and the subsequent steps are dependent on tissue-specific enzymes.

Prostanoids are important inflammatory mediators. We emphasize the importance of prostaglandins PGE₂ and PGI₂, as they are potent vasodilator agents in addition to potentiating the increase in permeability induced by mediators such as histamine and bradykinin.¹⁰ Moreover, due to bradykinin and histamine potentiation, these PGs are also involved in hyperalgesia.¹¹ Prostanoids exert their effects through G-protein coupled receptors,¹² activating different intracellular signaling pathways.

In the early 70's, Flower and Vane¹³ demonstrated that acetaminophen was capable of inhibiting COX activity in the brain much more efficiently than in other tissues. This study supported the theory that there is a variant of the COX enzyme in the brain, and that acetaminophen is a selective inhibitor of this enzyme, identified in the cerebral cortex of dogs and called COX-3; it is, however, an alternative splice of COX-1.¹⁴

NSAIDs relieve pain, fever, and inflammation by inhibiting COX enzyme.¹⁵ In turn, NSAIDs are divided into traditional and selective inhibitors. The latter selectively inhibit COX-2 and appeared in order to reduce gastrointestinal effects of traditional inhibitors. However, this selectivity results in an imbalance between anti- and pro-thrombotic factors, with a predominance of thromboxane (TXA₂) at the expense of prostacyclin (PGI₂), which triggers a series of cardiovascular complications.

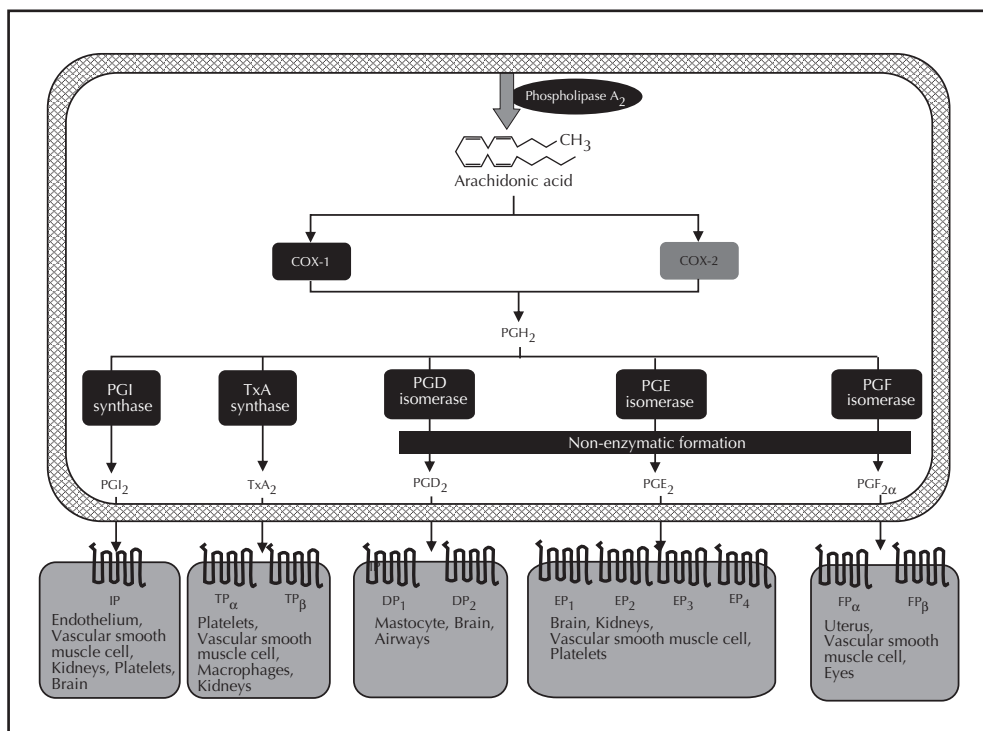


Figure 1 Mediators derived from cyclooxygenase (COX) and site of action. Arachidonic acid, which is normally esterified to membrane phospholipids, is released by the action of phospholipase A₂ enzyme. Once released, arachidonic acid can be converted to several biologically active compounds by the initial action of COX-1 or COX-2 enzyme and sequentially, by other tissue-specific enzymes and also by non-enzymatic mechanisms. The produced prostanoids (PGE₂, PGF₂, PGD₂, PGI₂ and TXA₂) exert their main effects by the activation of 7-transmembrane receptors. Adapted from Grosser et al.²¹

SELECTIVE COX-2 INHIBITORS: RISE AND FALL

Gastrointestinal complications are recognized as the main limitation for the chronic use of NSAIDs. These complications are mainly due to the inhibition of prostanoids produced by COX-1, which are responsible for gastric epithelial cytoprotection.^{16,17} Thus, the demonstration of the existence of a second enzyme, which differently from COX-1 did not seem to be constitutively expressed in tissues and of which expression was induced by inflammatory mediators, generated great enthusiasm.¹⁸

Considering the new facts, it was suggested that the COX-2 was the main, if not the only, source of prostaglandin production during the inflammatory process.¹⁸ Meanwhile, COX-1, which is constitutively expressed in many tissues, was considered primarily responsible for homeostatic functions and the only isoform involved in gastroduodenal mucosal protection.¹⁶ This fact led to the hypothesis that COX-2 selective inhibition had anti-inflammatory, analgesic and antipyretic effects, without the gastrointestinal toxicity of traditional anti-inflammatory drugs. This hypothesis directed the search for and the development of selective drugs for COX-2.¹⁹

In 1999, less than a decade after the discovery of COX-2,²⁰ the first selective COX-2 inhibitors (Coxibs), celecoxib and rofecoxib, entered the market. In 2001, the sales volume of rofecoxib reached US\$ 2.5 billion in the market in 80 countries, thanks to its dynamic marketing campaign.^{4,21,22} Lumiracoxib and etoricoxib emerged as the second generation of Coxibs²³ (Table 1).^{24,25}

Despite of the great and fast success of Coxibs, it soon became apparent that selective COX-2 inhibition was much more complex than what was suggested by the simplistic initial

hypothesis. Controlled clinical trials showed that Coxibs increase the risk of cardiovascular complications,^{15,26–28} affecting approximately 1%–2% patients a year included in randomized controlled trials. These data led to the withdrawal of rofecoxib in 2004, followed by valdecoxib in 2005.²⁹ It is estimated that rofecoxib caused nearly 28,000 heart attacks and sudden deaths in the United States between 1999 and 2003.³⁰ Some studies also indicate that, together, rofecoxib and celecoxib have caused more than 26,000 deaths during the first five years of their release in the U.S. market.³¹

The withdrawal of rofecoxib from the market by Merck in 2004 was followed by a heated debate in the scientific and popular press about the use and safety of Coxibs.^{29,30,32} This case disclosed the deficiency that can precede the approval of a drug. The approval of the first three Coxibs (celecoxib, valdecoxib and rofecoxib) was based on clinical studies of short duration and with only a few hundred volunteers.^{33–36} Interestingly, the possibility of cardiovascular risks caused by these drugs had already been anticipated, even before the approval of the first class representatives.^{37,38} Moreover, increased cardiovascular risk with rofecoxib was already visible in the initial clinical trial,³⁹ and yet further studies were carried out, which exposed patients to this risk for a prolonged period of time.

It is noteworthy, however, that although the Coxibs are associated to a lesser extent to adverse effects on the digestive system, data from the literature suggest that selective COX-2 inhibitors are not devoid of such effects. These drugs are associated with the loss of healing activity in patients who already have ulcers, as well as decrease in protective activity against invading microorganisms into the bloodstream, such as *Helicobacter pylori*.⁴⁰ In an observational study, it was

Table 1
Selective COX-2 Inhibitors

Compound (commercial name)	Year of appearance	Situation	Oral bioavailability	Half-life (h)	T max (h)	IC ₅₀ Ratio ³
Rofecoxib ¹ (Vioxx)	1999	Removed in 2004	92%–93%	17	2–3	272
Celecoxib ¹ (Celebra)	1999	Available in market	22%–40%	12	2–4	30
Valdecoxib ¹ (Bextra)	2001	Removed in 2005	83%	8	2–3	51
Parecoxib ¹ (Bextra IM/IV-pro-drug of valdecoxib)	2001	Hospital use only	—	0.3	IV: 0.04 IM: 0.2	51
Etoricoxib ² (Arcoxia)	2002	Dose of 120 mg removed in 2008	100%	22	1	344
Lumiracoxib ² (Prexige)	2005	Removed in 2008	74%	4	2–3	700

¹1st generation of Coxibs; ²2nd generation of Coxibs; ³Ratio of values of Cl₅₀(Cl₅₀ COX-1/Cl₅₀ COX-2; the higher the value, the higher the COX-2 selectivity). Cl₅₀: necessary concentration of the drug to inhibit 50% of COX-1 or 50% of COX-2.
Adapted from Hinz et al.,²⁴ and Patrignani et al.²⁵

demonstrated that patients with a previous history of ulcers and gastrointestinal complications associated with the use of traditional anti-inflammatory drugs may have the same adverse effects when using selective COX-2 inhibitors.⁴¹ The risk of gastric ulcers was reduced, but not eliminated.⁴²

Currently, in Brazil, only celecoxib and etoricoxib are commercialized, both with prescription retention and clear indication of cardiovascular complication risks.⁴³

BIOLOGICAL BASIS FOR CARDIOVASCULAR COMPLICATIONS

As described initially, the prostanoids are a family of bioactive lipid mediators produced by COX from arachidonic acid. PGI₂, one of the most important prostanoids in the control of homeostasis of cardiovascular system, is a potent vasodilator and additionally, inhibits platelet aggregation, leukocyte adhesion and proliferation of vascular smooth muscle cells. Therefore, PGI₂ has a protective effect in the atherogenic process. The effects of PGI₂ contrast with those of TXA₂, which cause platelet aggregation, vasoconstriction and vascular proliferation (Figure 2).²⁷ Thus, the balance between TXA₂ produced by platelets and PGI₂ produced by endothelial cells is crucial for cardiovascular health.^{44,45}

The first evidence of the importance of the balance between TXA₂ and PGI₂ came from studies with aspirin. Aspirin irreversibly inhibits COX-1 through the acetylation of the active site of the enzyme. Unlike endothelial cells that can synthesize a new COX-1 enzyme in a few hours, the platelet is devoid

of nucleus, making it unable to restore the inhibited enzymes. Thus, aspirin permanently inhibits the metabolism of arachidonic acid by platelet COX-1. It is also important to remember that the platelet does not have COX-2. Thus, regular doses of aspirin cause a cumulative and almost complete inhibition of platelet COX-1, barely affecting endothelial COX. Stated in another way, aspirin reduces TXA₂ formation by the platelet with minimal effect on PGI₂ production by endothelial cells. This production shift in favor of PGI₂ generates an antithrombotic environment, which has already been well-documented. The daily use of low-dose aspirin in patients at risk reduces the occurrence of thrombotic events.⁴⁶

According to the initial hypothesis that COX-2 is not constitutively present in tissues, being expressed only during the development of an inflammatory response, it is logical to assume that, in individuals presenting no vascular inflammation, the selective inhibitors of this enzyme would not affect the balance between PGI₂ and TXA₂.

However, it soon became evident that COX-2 was expressed not only during inflammation, but could be present in several tissues during physiological conditions,⁴⁷ including vascular cells.⁴⁸ Studies in healthy volunteers have shown that selective COX-2 inhibitors reduce prostacyclin (PGI₂) formation.^{37,38} Taken into account with other studies,^{49,50} these data indicate that 60%–70% of PGI₂ production in healthy humans is derived from COX-2. Thus, COX-2 would be the predominant COX isoform in the vascular endothelium, and would be directly associated with prostacyclin production in normal circulation. This view differs from the initial hypothesis that COX-2 was expressed only during inflammation. Corroborating this idea, some studies have shown that shear stress, which is constantly created by the pressure and movement of blood within the vascular lumen, may cause COX-2 expression (Figure 3).^{51,52} This would explain the absence of COX-2 in cultured endothelial cells,⁶ as they are not exposed to mechanical stress.

However, despite the evidence indicating that COX-2 can be an enzyme constitutively expressed on endothelial cells, these findings are not uniform. Several studies using immunohistochemistry analysis have shown that blood vessels of healthy individuals express COX-1, with minimal evidence of constitutively expressed COX-2.^{53–55}

Nonetheless, if on the one hand there is no consistent evidence of constitutive expression of COX-2 in healthy vessels, on the other hand there seems to be no doubt of an induction in COX-2 expression in atherosclerotic lesions. Interestingly, the urinary excretion of PGI₂ metabolites increases in patients with acute coronary syndrome⁵⁶ or soon

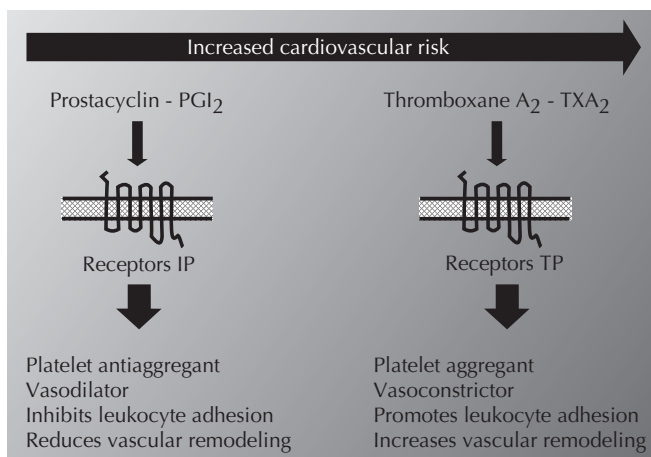


Figure 2
Vascular effects of prostacyclin (PGI₂) and thromboxane A₂ (TXA₂). Prostacyclin and thromboxane have opposite effects on the cardiovascular system.
Adapted from Mitchell; Warner.⁴

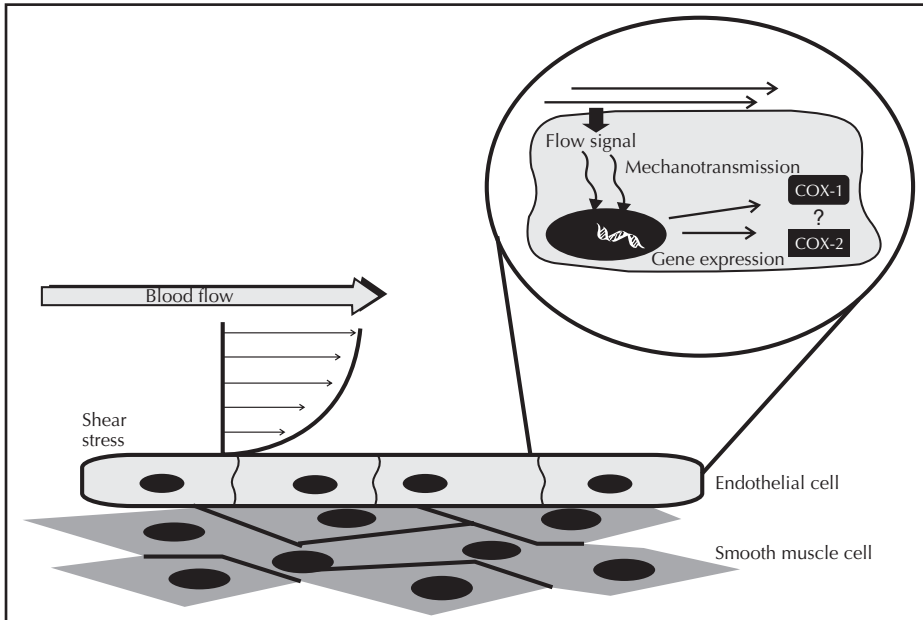


Figure 3 Shear stress effect (parallel to the surface of endothelial cells) generated by blood flow. The mechanical stimulus generated by blood flow in the endothelial cell can activate signal transduction factors, which in turn can lead to increased COX expression.

after a vascular intervention,⁵⁷ which can be interpreted as a vascular defense mechanism to prevent thrombotic events. Corroborating this idea, several studies showed COX-2 expression in atherosclerotic lesions.^{54,55,58} Platelets do not express COX-2 – then, as expected, COX-2 inhibitors do not inhibit TXA₂ production by platelets. The conclusion from these observations is that inhibition of PGI₂ production from COX-2 may generate an imbalance in the relationship between TXA₂ and PGI₂, thus increasing the probability of a thrombotic event (Figure 4).

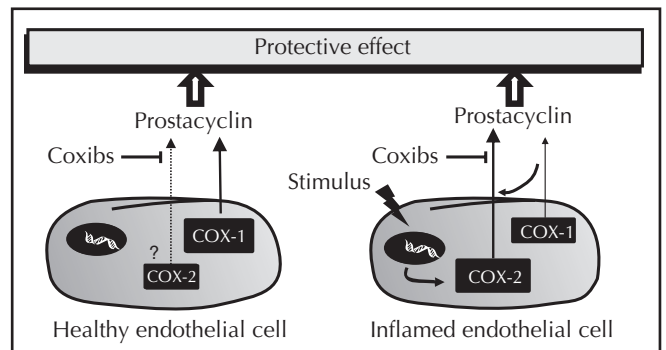


Figure 4 Balance between pro-atherogenic and anti-atherogenic mediators. In a normal state (healthy endothelial cell), PGI₂ production is largely dependent on COX-1. However, in a vascular injury situation (inflamed endothelial cell), COX-2 expression is induced in endothelial cells, contributing to PGI₂ production, in opposition to the atherogenic effects of TXA₂ produced by COX-1 from the platelets. The use of selective anti-inflammatories for COX-2 (Coxibs) may reduce PGI₂ production, generating an imbalance between TXA₂ and PGI₂.

CARDIOVASCULAR RISKS WITH TRADITIONAL NSAIDS

The selectivity for COX isoforms can be seen as a continuous variable among the drugs that inhibit these enzymes;¹⁵ there is no absolute selectivity for either isoform. Even a selective inhibitor for COX-2 will also inhibit COX-1 at sufficiently high concentrations.²¹ Moreover, some drugs said to be non-selective at low concentrations, such as diclofenac, selectively inhibit COX-2.²¹ Yet, in spite of being classified as a traditional NSAID, this drug has COX-2 selectivity that is similar to that of celecoxib.⁵⁹ Therefore, all anti-inflammatory drugs, selective COX-2 inhibitors or not, can be associated, albeit at different degrees, with an increased risk of cardiovascular adverse events.⁶⁰

The Food and Drug Administration draws attention to the fact that both selective and nonselective inhibitors can increase

the risk of cardiovascular disorders.⁶¹ Epidemiological data suggest that both Coxibs and traditional NSAIDs have the potential to trigger heart problems, especially when used at high doses and for long periods of time. Thus, the risks (cardiovascular) and benefits (GI) of Coxibs should be taken into consideration, and their indication should be individualized to each patient.²⁸

In a meta-analysis that assessed the risk of cardiovascular events with the chronic use of anti-inflammatory drugs, diclofenac and ibuprofen (traditional non-selective drugs), as well as etoricoxib and lumiracoxib (COX-2 selective drugs) increased the odds of cardiovascular events by more than 30%. This study evaluated 31 randomized clinical trials, in which they evaluated the cardiovascular risk of seven NSAIDs: ibuprofen, diclofenac, etoricoxib, rofecoxib, naproxen, celecoxib and lumiracoxib.⁶⁰

Regarding the risk of cerebrovascular disorders, non-selective inhibitors showed to be more deleterious than the selective ones. Ibuprofen (which belongs to the class of traditional anti-inflammatory drugs) showed a 3.36-fold higher chance for the occurrence of the event, vs. 2.86 for diclofenac, 2.67 for etoricoxib and 1.76 for naproxen.

As for the risk of cardiovascular death, etoricoxib showed a higher chance for the occurrence of the event (4.07 times), followed by diclofenac (3.98), ibuprofen (2.39), celecoxib (2.07), lumiracoxib (1.89) and rofecoxib (1.58). These data show that the cardiovascular risk is not restricted to selective COX-2 anti-inflammatory drugs.⁶⁰

McGettigan and Henry,⁶² in their meta-analysis, agree with the fact that there is cardiovascular risk with traditional inhibitors. The authors even showed that some traditional NSAIDs can be more deleterious than Coxibs. In this study, diclofenac showed relative risk for cardiovascular events of 1.40 (considering the observational studies), a higher risk than that demonstrated for celecoxib, of which risk was 1.01.⁶² Together with this deleterious cardiovascular effect also associated with traditional inhibitors, patients with arthritis treated with diclofenac showed identical rates of thrombotic cardiovascular events when compared to patients who received etoricoxib.⁶³

It is also important to remember that both traditional NSAIDs and Coxibs, albeit in different proportions, increase blood pressure in a dose-dependent manner.^{26,64} This effect is a consequence of hydroelectrolytic balance alterations and vascular reactivity.⁶⁵ Nevertheless, the increase in blood pressure, regardless of the risk of thrombosis, may contribute to an increased risk in cardiovascular complications due to the use of these drugs.

However, there is still a lack of controlled randomized, large-scale clinical trials, for several of the traditional NSAIDs, making it difficult to obtain conclusive findings about the risk of cardiovascular complications that occur with the use of these drugs.

We must also remember that NSAIDs are a group of rather heterogeneous chemical compounds, so it is not surprising that

each individual compound has different characteristics with the potential to affect their risk-benefit ratio, such as half-life, potency and COX-2 selectivity. All these drug-inherent factors integrate with basal cardiovascular risk to determine the likelihood of cardiovascular complications in patients.²¹ Thus, results obtained with a particular drug cannot be readily shared with all class of NSAIDs.

This dynamic association between the pharmacological properties of a drug with cardiovascular risk is well illustrated by diclofenac. Diclofenac has a short half-life (1–2 hours) and therefore it is prescribed in large doses to produce the drug concentration deemed necessary for an effective anti-inflammatory and analgesic effect between dose intervals. As diclofenac is one of the most potent COX inhibitors and has reasonable COX-2 selectivity, even similar to that of celecoxib, its plasma concentration exceeds by several times the concentration required to inhibit only COX-2, also inhibiting COX-1.¹⁹ With the elimination of the drug and consequent decrease in plasma concentration, COX-2 inhibition remains, whereas COX-1 inhibition disappears.⁶⁶ The discordant rates of COX isoform inhibition *in vivo* results in a small selectivity window for COX-2, called the risk window.¹⁵ Drugs such as ibuprofen and naproxen do not have this window, as their COX-1 inhibition exceeds that of COX-2 during the entire time interval between doses.²¹

The cardiovascular risks of selective COX-2 inhibitors are yet to be elucidated; thus, no cardiovascular risk prediction may be based on this selectivity⁶⁰ and it is not possible to affirm that the use of a traditional inhibitor is safe regarding this adverse effect.

Sheinberg⁶⁷ criticizes the fact that there is greater control only for selective inhibitors. It is worth remembering that the gastrointestinal risks of non-selective anti-inflammatory drugs are as severe as cardiovascular risks of selective inhibitors; both can be potentially fatal. Actions such as retaining the Coxibs prescription and the less restrictive sales of non-selective inhibitors erroneously suggest that the latter do not have risks, and also make their use indiscriminate.⁶⁷

PERSPECTIVES FOR THE USE OF SELECTIVE COX-2 INHIBITORS

COX is the most common target of anti-inflammatory drugs.⁶⁸ In clinical practice, choosing a traditional NSAID or Coxib has always been a challenge.⁴² For cases of acute pain in patients with a history of gastrointestinal complications,

Coxibs are an excellent choice, as their use for a short period of time brings no risk of gastrointestinal or cardiovascular complications.¹⁵ For instance, in cases of primary dysmenorrhea, orthopedic surgeries and dental procedures, where the use of anti-inflammatory drugs usually do not exceed one week, Coxibs can be a safe and effective option for many patients.

It is noteworthy the fact that the cardiovascular risks associated with Coxibs (present when there is chronic use) does not make them less indicated than nonselective inhibitors, as the latter are also associated with cardiovascular events⁶⁰ and their gastrointestinal risks are as severe as the possible cardiac risks with Coxibs.⁶⁷

CONCLUSION

Considering the increasing use of anti-inflammatories, it is worth noting that selective inhibition of COX-2 arose in order to eliminate the undesirable effects of non-selective inhibition of COX, such as gastrointestinal adverse events. In contrast, the decrease (not elimination) of gastrointestinal side effects resulted in the appearance of cardiovascular events. Considering the pros and cons of both classes of COX inhibitors, both are valid options as anti-inflammatory drugs. However, each case must be analyzed, as well as the particularities and needs of each patient, aiming to attain the correct indication of each class of COX inhibitors.

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