



Selective cyclooxygenase-2 inhibitors in dentistry: limitations and adverse effects

Gleicy Fátima Medeiros de Souza^a, Luciano Cruz de Barros Caldas^b, Gessyca Suielly Melo Matos da Silva^c

Abstract

The coxibs are nonsteroidal anti-inflammatory drugs (NSAIDs) highly selective for COX-2, an enzyme related to inflammatory processes. At first, their use should present advantages over non-selective NSAIDs, since the inflammatory efficacy would be present but with minimal adverse effects. However, its widespread use showed significant cardiovascular risk and, in treatment over 6 months, predisposition to ulceration, bleeding and stomach pain. The coxibs should be used in patients over 60 years, with a history of peptic ulcer or gastrointestinal bleeding, chronic users of corticosteroids and anticoagulants without concomitant cardiovascular risk. Moreover, they are more expensive and have similar analgesic efficacy to non-selective NSAIDs. In dentistry, the main indications are related to the control of pain and inflammation for a maximum of 3 days or preemptively in oral surgery to control pain and swelling. However, there is no major evidence of the benefits of using these drugs compared to traditional NSAIDs in dentistry.

Key words: Dentistry; Anti-Inflammatory agents; Cyclooxygenase 2 inhibitors; Adverse effects; Therapeutic use; Contraindications

^a Pernambuco University, Camaragibe, Brazil

^b Governador Paulo Guerra Hospital, Recife, Brazil

^c Associação Brasileira de Odontologia de João Pessoa, João Pessoa, Brazil

Inibidores seletivos da cox-2 na odontologia: limitações e efeitos adversos

Resumo

Os coxibes são antiinflamatórios não-esteroidais (AINEs) altamente seletivos para a COX-2, enzima relacionada à processos inflamatórios. A princípio, seu uso deveria apresentar vantagens em relação aos não-seletivos, pois permaneceria a eficácia antiinflamatória com um mínimo de efeitos adversos. Entretanto, sua ampla utilização revelou significativo risco cardiovascular e, em tratamento acima de 6 meses, predisposição à ulcerações, hemorragias e dor gástricas. Sendo recomendado seu uso em pacientes acima de 60 anos, com histórico de úlcera gástrica ou hemorragia digestiva, usuários crônicos de corticostéoides e anticoagulantes. Além disto, são mais caros e possuem eficácia analgésica similar aos AINEs não-seletivos. Em odontologia suas principais indicações estão relacionadas ao controle da dor e da inflamação pelo período máximo de 3 dias ou preemptivamente em cirurgias orais para controle da dor e edema. Entretanto, não há evidências de maiores benefícios da utilização destes fármacos em relação aos AINES tradicionais no manejo odontológico.

Palavras-chave: Odontologia; Antiinflamatórios; Inibidores de ciclo-oxigenase 2; Efeitos adversos; Uso terapêutico; Contra-indicações

Correspondence:

Gleicy Fátima Medeiros de Souza
gleicyfop@yahoo.com.br

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Introduction

Clinical management of inflammatory symptoms constitutes one of the most common actions in the dental routine, and control of clinical symptoms, especially pain and fever, is based on the use of non-steroidal anti-inflammatory drugs (NSAIDs). These drugs act on the prevention or control of inflammatory and clinical events, by interfering in biochemical production of proinflammatory prostaglandins [1,2].

The NSAIDs are an ample group of drugs with anti-inflammatory, antipyretic and analgesic properties, which appeared around the 60s as an alternative to aspirin. They consist of the top sold drugs worldwide and, together with analgesics and antipyretics, amount to about 30% of the drugs commonly used in clinical practice [3].

NSAIDs work by inhibiting the cyclooxygenase (COX) enzyme, responsible for the synthesis of prostaglandins (PGs) from arachidonic acid. Its modulation is the essence of these drugs action mechanism, resulting in its ability to control the inflammation, pain and fever. There are at least two COX isoforms: COX-1 and COX-2. The Type 1 is constitutively expressed, mainly found under physiological conditions, in cells and tissues such as blood vessels, platelets, stomach and kidneys. The generated prostaglandins are mostly involved in physiological processes. The COX-2 can be induced in the presence of cytokines, growth factors and endotoxins, and is characteristically expressed by cells and tissues involved in the inflammatory process, such as macrophages and monocytes. All of the NSAIDs inhibit both enzymes but with varying degrees of intensity and specificity [4,5].

Inhibition of COX-1 is associated with an increased risk of bleeding and gastrointestinal disorders. In an attempt to reduce the incidence of these effects, with the same anti-inflammatory and analgesic efficacy, the highly selective COX-2 inhibitors, or Coxibs, were developed. However, despite the low gastrointestinal risk, evidence shows that their clinical use should be cautious due to their high cardiovascular risk, which can lead to heart failure, hypertension, myocardial infarction and stroke. Such events are a result of this selectivity that provides an unbalance between anti- and pro-thrombotic factors, with the action of thromboxane (TXA₂) predominating at the expense of prostacyclin (PGI₂), a potent vasodilator and platelet anti-aggregant, which triggers a series of cardiovascular complications. Among these drugs are the celecoxib, etoricoxib, valdecoxib, parecoxib and lumiracoxib [6,7,8,9].

Pharmacological knowledge of various groups of drugs is critical for the dentist, not only for the act of prescribing, but also to allow safe clinical management by preventing or minimizing the risk of adverse effects and drug interactions. Thus, the present study aims to update the literature on the Coxibs and their main limitations and adverse effects in dentistry.

Coxibs in Dentistry: An Update

The COX-2 enzyme plays a crucial role on the bone healing process, being induced in the early stages as a

result of the increase, mainly, of prostaglandin E₂ (PGE₂), playing an important role in the regulation of bone formation and absorption. Pharmacological interventions with anti-inflammatories, such as highly selective COX-2 inhibitors, are potentially able to interfere with the inflammatory process, bone resorption and remodeling, considering that they can inhibit or significantly alter tooth movement, bone healing and fracture healing [4,10].

However, the results have been clinically conflicting. Studies have sought to observe if the different balance of COX-1/COX-2 inhibition in highly selective NSAIDs would interfere less or not at all on bone healing and tooth movement. Some authors point out the Coxibs as a source of disorder in orthodontic treatment capable of interfering in the tooth movement process [11], while others have not seen such effect [12,13].

De Carlos et al. [14] evaluated orthodontic movement after use of different therapies with COX-2 inhibitors in rats and found that celecoxib and parecoxib, avoided interference in tooth movement, being considered appropriate for use, but that rofecoxib was not.

On the other hand, PGE₂ produced by COX-2 in bone diseases can stimulate bone resorption, increasing the number and activity of osteoclasts, thus, playing an important role in bone loss in diseases such as periodontitis and peri-implantitis [15].

Azoubel et al. [16] found no improvement in the clinical parameters regarding the use of Etoricoxib 120 mg/day, but verified the reduction of PGE₂ levels in crevicular fluid, which could be related to the slight improvement in bone condition in the non-surgical treatment of aggressive periodontitis. Yen et al. [15], in a study with 131 patients for the treatment of chronic periodontitis, found that celecoxib is an effective drug in addition to scaling and root planing, providing better treatment outcomes by reducing the progression of bone loss.

An important point made by Bergamaschi et al. [17] and Bortoluzzi et al. [18] refers to the adverse effects of chronic use of Coxibs. The authors note that recommendations for pain management and inflammation in dentistry endorse its use for a maximum of 4 to 5 days, which rarely triggers adverse effects in healthy individuals.

Such considerations are corroborated by Franco et al. [10], who recommend the use of Coxibs in dentistry for a period of 48 and 36 hours, for the control of pain and inflammation, respectively. There is no evidence of a greater benefit from its use compared to other NSAIDs, and its risks and benefits, as well as the clinical profile of the patient need to be considered when prescribing these drugs [8].

In patients with congestive heart failure, liver cirrhosis, chronic kidney disease, hypovolemia and other conditions that activate the simpaticoadrenal and renin-angiotensin systems, there is increased expression of prostaglandins in the kidney. These PGs, produced by COX-2, are capable of vasodilating properties and are responsible for maintaining the balance of vasoconstriction substances, the renal blood flow and glomerular filtration rate [19]. The use of selective

or non-selective NSAIDs in these patients promotes the blocking of the renal prostaglandin synthesis, reducing glomerular filtration and renal blood flow. The result is inhibition of renal excretion of water and salts, which leads to acute renal failure, hypertension, peripheral edema and hypercalcemia [3,9,20].

Within the context of the cardiovascular system, the negative influence of Coxibs is related to the blockade of PGI₂ synthesis, thus setting a deviation on the PGI₂ / TXA₂ balance in favor of TXA₂, triggering a vasoconstrictor, pro-platelet effect, promoting leukocyte adhesion and stimulating vascular remodeling. This imbalance results in high blood pressure and risk of thrombus formation, which tend to increase with the progression of the treatment, with a higher incidence of ischemic events after a few months of use of these drugs [7,8,9].

According to Epstein [190], in patients with cardiovascular risk, such as patients who have suffered myocardial infarction or revascularization, drugs such as Coxibs should not be prescribed, taking into account the high risk of heart attack and stroke, as well as the development of life-threatening skin reactions such as Stevens-Johnson syndrome. The Food and Drug Administration (FDA) has recommended the suspension of the marketing of oral valdecoxib (Bextra[®]), considering that the drug showed no clear benefit when compared with non-selective NSAIDs [21].

In the same way Berger, Dwyer and Corallo [22] state that patients with a history of asthma, urticaria or allergic reactions after taking acetylsalicylic acid or other NSAIDs should not make use of Celebra[®], with the drug associated with erythema multiforme reports, Stevens-Johnson syndrome and toxic epidermal necrolysis.

ANVISA [21] and Shi and Klotz [23] and find that the risk of cardiovascular effects resulting from the use of Coxibs is dose and interval dependent. In patients with cardiovascular risk, Naproxen produces safer and more effective results, becoming a better alternative than Coxibs. However, De Jean et al. [24] found that the preventive use of Coxibs in oral surgery does not cause damage to the cardiovascular system, due to the short time of use.

Hinz and Brune [25] show that the Coxibs have important indication in patients over 60 years, with gastric ulcer or gastrointestinal bleeding history, corticosteroid users for a long time and anticoagulants. However, these should not present concomitant cardiovascular risk. These recommendations are based on the preferential inhibition of PG's by coxibs, which are regulated by COX-2. A fact that contributes to a lower rate of gastrointestinal complications such as dyspepsia, ulcers, intestinal perforations and duodenal [6,8,21,26].

However, conflicts have been observed regarding the gastroprotective effect of Coxibs, as the occurrence of ulcers and gastrointestinal complaints in the short term treatments, up to 6 months, was reduced but not eliminated. It is highlighted that, as the treatment time progresses, there is an increase of gastric risk, especially gastropathy, petechial hemorrhages, dyspepsia, abdominal pain and

diarrhea [27,28]. According to Mendes et al (2012) [8], Garcia Jr. et al. [29] and Hilary et al. [30], the use of Coxibs in dentistry would only be justified in patients with proven medical history of gastrointestinal disorders without concomitant risk of cardiovascular disorders.

The important cardiovascular effects led the National Agency for Sanitary Surveillance (ANVISA) to cancel the registry of rofecoxib (Vioxx[®]) in 2004 and of lumiracoxib (Prexige[®]) and etoricoxib 120mg (Arcoxia[®]) in 2008. and restrict the use of parecoxib (Bextra[®] IM / IV) to hospitals. Currently, Coxibs that remain in the market are Celecoxib (Celebra[®]) Etoricoxib 60 mg and 90 mg (Arcoxia[®]), Parecoxib (Bextra[®] IM/IV) and oral Valdecoxib (Bextra[®] VO), but with the knowledge that the risks of their use outweigh their benefits [8,21,31].

An important point to note is the use of coxibs in pregnant and lactating women. Ostensen and Skomsvoll [32] point out that non-selective and selective COX-2 NSAIDs, are contraindicated in pregnant women, at the risk of causing stenosis of the ductus arteriosus, oligohydramnios and postpartum hemorrhage. In turn, the transfer of substances into breast milk depends on several factors, such as chemical composition and use of medications. Such factors may facilitate the passage of drugs into milk or contribute to its greater permanence in the body of the lactating, which can lead to toxicity [33].

It should be noted that the exposure to drugs in infants is one of the factors responsible for early weaning. Many doctors and dentists hold little information about the use and safety of medicines during lactation, preferring to indicate the suspension of breast feeding to not run the risk of harming the child [34].

Hale et al. [35] found a milk/plasma ratio for celecoxib of 0.23, ranging from 0.15 to 0.31, being considered low infant exposure dose, corresponding to 0.3% of the maternal dose. Knoppert et al. [36] on a case study with a patient who received 4 oral doses of celecoxib 100 mg, found that 5 hours after the last dose the milk concentration of celecoxib was 133 ng/ml and half-life of elimination was 4.0 to 6.5 hours. Celecoxib had the advantage of its low concentration in breast milk, but its half-life of elimination is high, which may predispose to risk. Due to the absence of conclusive evidence on the efficacy of coxibs, ANVISA does not recommend its use in children [21].

With regard to drug interactions, selective or not NSAIDs, may cause reduction in the effect of antihypertensive agents due to their activity in kidney and/or cardiovascular level. Extra care should be taken in patients taking antihypertensives that require prostaglandin synthesis to produce vasodilating effect, such as inhibitors of angiotensin converting enzyme. And, because of the pro-thrombotic activity of Coxibs, drug interactions may occur with warfarin, aspirin or other anticoagulant drugs [5,37].

In general, the Coxibs are metabolized by enzymes of the microsomal liver system cytochrome P450 (CYP450). Therefore, clinical monitoring during co-administration with drugs that inhibit the enzyme CYP2C9 (fluconazole,

phenytoin, valproic acid, lithium, and selective serotonin reuptake inhibitors) and metabolized by the enzyme CYP2D6 (tricyclic antidepressants, neuroleptics, phenobarbital) is important. These are situations in which the increase or decrease in serum concentration of Coxib or other concomitant medication taken by patients may occur [38].

With regard to the clinical use of Coxibs, they present the same indications of non-selective and preferential selective NSAIDs, being used in post-operative pains and inflammatory in nature. The difference between what kind of NSAID (selective, preferential selective, highly selective or non-selective) will be prescribed must respect the systemic conditions of the patient. Other acute and chronic conditions that coxibs are indicated are: odontogenic and post surgical pain, dysmenorrhea, acute conditions, primary dysmenorrhea, musculoskeletal and joint disorders such as arthritis and rheumatic diseases, and as an adjuvant in cancer treatment [39,40].

Sotto-Maior et al. [41] found that etoricoxib 120 mg and dexamethasone 4 mg, administered 1 hour before third molars surgery showed no statistically significant differences in pain and postoperative edema. Similarly, Cicconetti et al. [42] found that Coxibs are as effective as non-selective NSAIDs in controlling post-oral surgery pain. Steffens et al. [43] also found that both Coxibs and NSAIDs are effective in preventing pain, swelling and discomfort following periodontal surgery.

Therefore, the choice and clinical prescribing of the most appropriate anti-inflammatory should be based on the lowest frequency of use, minimum intensity of adverse effects and cost of medication, because there are no categorical evidence that demonstrates the effectiveness of highly selective anti-inflammatory over the others [8,30].

Final Considerations

Despite the early promise as an excellent analgesic, there are still insufficient evidence in the literature to support the Coxibs as the first pharmacological option for the control of pain and inflammation in dentistry. These drugs are expensive and have analgesic efficacy similar to non-selective NSAIDs. They also have an increased cardiovascular risk and, in treatment over 6 months, predispose ulcerations, bleeding and stomach pain.

The main uses of Coxibs in dentistry are related to the control of pain and inflammation for a maximum of three days or pre-emptively in oral surgery to control pain and swelling. However, there is no evidence of greater benefits in these drugs in dentistry compared to traditional NSAIDs.

It is noteworthy that coxibs have important indication in patients with high gastrointestinal risk for short-term treatment, especially in individuals over 60 years, with gastric ulcer or gastrointestinal bleeding history, corticosteroid users for a long time and anticoagulants. However, they should not present concomitant cardiovascular risk. For patients that present gastrointestinal, as well as cardiovascular risk, non-

selective NSAIDs association with proton pump inhibitors is a safer choice than coxibs.

To date there is not enough clinical studies to safely support the use of coxibs in pregnant women, nursing mothers and children under 18, except for etoricoxib, which is allowed for patients over 16 years.

Finally, the prescription should be based on the individual. It is crucial to analyze each patient in order to establish an appropriate and safe prescribing, considering the risks and benefits of this class of drugs as well as the alternative use of other pharmacological classes.

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