

Selective Cox-2 Inhibitor

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ABSTRACT:

NSAIDS (NON-steroidal anti-inflammatory drugs) are commonly used medications in dental and medical practice. Their uses in dentistry include use as analgesics, as anti-inflammatory agents and has anti-pyretic actions. The common side effects of this class of medications are gastrointestinal irritation with potential for ulceration, increased tendency for bleeding due to antiplatelet effects, and long-term chronic dosing effects on renal function may occur. Recent introduction in anti-inflammatory groups is the introduction of cyclooxygenase 2 inhibitors. COX-2 inhibitors offer substantial benefits because of their favorable gastrointestinal profiles and because of their lack of effect on platelet function. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;92:399-405).

KEYWORDS : NSAIDS, CELECOXIB, ROFECOXIB, selective COX-2 inhibitors.

I. INTRODUCTION :

Pain is commonly associated with inflammation. Prostaglandins are mediators between pain and inflammation. (1,2 and 3)* In 1990, the enzyme cyclooxygenase was demonstrated to exist in 2 distinct isoforms, COX-1 and COX-2. COX-1 has been found to be constitutively expressed in most tissues of the human body and provides prostaglandins with a role in the homeostatic functions, including affecting gastric mucosa, renal blood flow, hemostasis, wound healing, and ovulation. (4)* By contrast, COX-2 maintains a low level of basal constitutive expression only in the brain neurons, kidneys, female reproductive system, and bone where it may be up-regulated, whereas in most tissues it may be inductively expressed by inflammatory cytokines and growth factors in response to inflammation and tissue injury (such as a surgical trauma). (5,6,7)* In animal studies, COX-2 has been inductively expressed within 2-4 hours after a trauma, and within 1-2 hours from surgery in the oral cavity—mucosa, thus leading to a rapid onset of the postoperative pain. (8)* The widespread popularity of NSAIDs, in combination with a high frequency of complications, has sparked pharmacologic research and publicity. In particular, a newer class of NSAIDs, selective cyclooxygenase-2 (COX-2) inhibitors have been developed as potentially safer alternatives to traditional nonsteroidal agents. (9,10,11,12,13,14,15)* COX-2 inhibitors have been licensed for the management of osteoarthritis, rheumatoid arthritis, and acute pain. (9,10,11,12,13,14,15)* The purpose of this article is to update dental providers on NSAIDs and new COX-2 inhibitors because this class of medication is expected to be frequently prescribed in medicine and dentistry.

II. MECHANISM OF ACTION OF NSAIDS:

NSAIDs are Non-Steroidal anti-inflammatory drugs. NSAIDs can be classified as ; 1. non-selective COX-1, COX-2, 2. Preferential COX-2, 3. Selective COX-1, COX-2. NSAIDs act by inhibiting COX conversion of arachidonic acid to prostaglandin, thereby reducing peripheral prostaglandin production. (16)* Until 1990, one COX enzyme was thought to exist, when the COX-2 isoform was discovered by Needleman et al. (2)* The products of arachidonic acid metabolism affect a variety of biologic processes, such as inflammation and hemostasis, and play important roles in renal, cardiovascular, and pulmonary systems. Arachidonic acid is liberated from the phospholipid membrane by phospholipase and is then metabolized by the lipoxygenase pathway to produce leukotrienes or by the cyclooxygenase pathway involving COX-1 and COX-2. COX-1 is constitutively found in the endoplasmic reticulum membrane of all cells and performs the “housekeeping” functions of prostaglandins (PG). Prostaglandins produced in the gastric mucosa via COX-1 increase mucus and bicarbonate secretion, mucosal blood flow, and turnover, as well as inhibit acid secretion. (17)* Thromboxane A₂ (TXA₂) production by platelets mediates platelet aggregation and vasoconstriction. PGE₂ production by vessel endothelium in conjunction with TXA₂ represents a fine balancing mechanism for modulating hemostasis. Ulcers are increasingly problematic when platelets are inhibited, potentiating hemorrhage and increasing blood loss. PG production in the liver and kidney regulates blood flow and can become problematic in “prerenal” conditions including hypovolemia, hypotension, and low cardiac output. (18)* COX-2 is found only in the brain, except when induced by growth factors and cytokines in inflamed tissue. Once induced, COX-2 is found on the endoplasmic reticulum and nuclear membranes of macrophages, leukocytes, fibroblasts, and endothelium. The prostaglandins produced by this mechanism promote the

vasodilation, pain, and fever characteristic of an inflammatory response. COX-2 likely inhibits both peripheral and central mechanisms of analgesia.(15)*

Nearly all NSAIDs marketed today inhibit both COX-1 and COX-2, and most have selectivity for COX-1. However, not all NSAIDs are equal: Some are better analgesics, others are more effective anti-inflammatories. They also vary greatly in the degree of side effects produced. A high ratio is most desirable because it implies that the compound is a relatively specific COX-2 inhibitor. Various studies demonstrates the ratio as ;

COX-2/COX-1 ratios of various NSAIDs :

Traditional NSAIDs:	COX-2/COX-1	ratio
Indomethacin		-1.78*
ASA		-3.12*
Ibuprofen		-1.78*
Naproxen		-0.88*
Ketorolac	(Toradol)	-0.68*
Selective COX-2		
Meloxicam-4		
Celecoxib	(Celebrex)	-7.0†
Rofecoxib	(Vioxx)	-36.0†
(19,24)*		

Because of the GI complications of nonselective NSAIDs, a number of approaches have been developed with the goal of decreasing GI toxicity. H2-receptor antagonists (ie, ranitidine), which suppress acid secretion, have been prescribed concurrently, but appear to offer inadequate protection. Prostaglandin analogues, the most common being misoprostol,(21)*may reduce GI symptoms from the NSAID but may cause diarrhea.(22)*Enteric coating of various NSAIDs and acetylsalicylic acid and inhibitors of acid production (eg, omeprazole/ Losec) may offer a limited advantage to GI irritation. Sucralfate is a viscous topical agent that lines the GI tract, but its efficacy in reducing GI toxicity due to NSAIDs is uncertain.(23)*Nitric oxide–releasing NSAIDs, zwitterionic phospholipids, and trefoil peptides are other potential means of preventing GI damage with NSAIDs. Nabumetone, a nonacidic prodrug, and etodolac have been called “preferential COX-2 inhibitors”; however, their improved GI safety appears to be due to properties other than selective COX-2 inhibition. Unfortunately, none of these approaches have been satisfactory.

SELECTIVE COX-2 INHIBITORS :

CSIs include celecoxib (Celebrex, Solexa, Artilog) and rofecoxib (Vioxx, Coxixil, Arofexx), which are both currently available in the United States and Europe, and second-generation agents, such as valdecoxib (Bextra), parecoxib (Dynasta, Rayzon, Xapit), etoricoxib (Arcoxia), and lumiracoxib (Prexige), which still are under investigation.

Pharmacological and clinical properties of COX-2-selective inhibitors:

- Drug name: CELECOXIB (47)
- [1] Brand name: Celebrex, Solexa, artilog.
- [2] Dosage: 100 or 200mg upto 3 times a day.
- [3] Route of administration : oral.
- [4] Adverse effects: nausea, headache, vomiting, dizziness, dyspepsia.
- [5] 2. Drug name: ROFECOXIB (55)
- [6] Brand name: Vioxx, cox ill, arofexx.
- [7] Dosage: 50mg/day loading dose.
- [8] Route of administration : oral.
- [9] Adverse effects: diarrhoea, headache, nausea, upper respiratory infection.
- [10] 3. Drug name: VALDECOXIB (32)
- [11] Brand name: bextra
- [12] Dosage: 40mg/day
- [13] Route of administration: oral
- [14] Adverse effects: nausea, vomiting, abdominal pain, dizziness, abdominal fullness.
- [15] 4. Drug name: PARECOXIB (34)
- [16] Brand name: Dynastat, rayzon, xapit.
- Dosage: 20-40mg/ day.
- Route of administration: Intra-venous or Intra-muscular.

CELECOXIB AND ROFECOXIB :

Celecoxib (the first Coxib developed) and rofecoxib have been licensed by the FDA for the management of inflammatory chronic pain of osteoarthritis, rheumatoid arthritis, and acute pain of primary dysmenorrhea. A number of trials of high quality have been performed in adults for the treatment of moderate to severe postoperative dental pain.(25)*In studies of postoperative dental pain, a single dose of celecoxib (200 mg) provided analgesic efficacy similar to that of aspirin (650 mg), and inferior to those of ibuprofen (400 mg) and naproxen (550 mg), as measured by time to onset of pain relief and peak pain relief; even at doses up to 400 mg, celecoxib was still inferior to naproxen (550 mg).(26,27,28,29)*Five studies of postoperative dental pain compared the analgesic efficacy of single doses of rofecoxib, celecoxib, ibuprofen, and naproxen.(30,31,32,33,34,35)*Those results demonstrated that rofecoxib (50 mg) was superior to celecoxib (200 mg) and similar to ibuprofen (400 mg) and naproxen (550 mg), as measured by total pain relief at 8 hours (TOPAR8) and time to onset of pain relief; the duration of analgesia provided by a single dose of rofecoxib (>24 hours) was longer than that provided by celecoxib (~5 hours) or ibuprofen (~9 hours). In one study of postoperative dental pain, a single dose of rofecoxib (50 mg) was superior to 3 doses of enteric-coated diclofenac (50 mg every 8 hours), as measured by TOPAR24 (assessment at 24 hours).(35)*In a study of moderate to severe postoperative dental pain, the analgesic efficacy of rofecoxib (50 mg) was greater than that of a fixed formulation of codeine (60 mg)/acetaminophen (paracetamol) (600 mg), as measured by TOPAR6. Findings from 6 placebo-controlled studies evaluating the single-dose analgesic efficacy of rofecoxib in the treatment of post-oral surgery pain support the recommended dose regimen of 50 mg of rofecoxib once daily, as compared to maximal analgesic daily-doses of naproxen (550 mg every 12 hours) and ibuprofen (400 mg every 4-6 hours).(24)Rofecoxib was recently approved in Europe for the treatment of acute pain (on PubMed: MMW Fortschr Med 2002 Mar 7;144(10):62 [no authors listed]).

VALDECOXIB:

In one trial of postoperative dental pain, a single oral dose of valdecoxib (40 mg) was superior to rofecoxib (50 mg) with respect to the onset of pain relief, duration of analgesia, and percentage of patients requiring rescue medication.(36)*In a similar study, valdecoxib (40 mg) showed an overall analgesic efficacy similar to that of a fixed formulation of oxycodone (10 mg)/acetaminophen (paracetamol) (1000 mg); valdecoxib was better tolerated and resulted in a duration of analgesia significantly longer than that of oxycodone/acetaminophen.(37)*In a meta-analysis of 8 randomized, controlled trials, the safety profile of valdecoxib was better than that of traditional NSAIDs, as displayed by a reduced incidence of adverse events.(38)*Valdecoxib has been shown to be effective in a study of preemptive analgesia for the treatment of post-oral surgery pain, thus demonstrating an inhibitory action of the constitutive COX-2 enzyme of the central nervous system.(39)*

PARECOXIB:

Parecoxib is the prodrug of valdecoxib and is the only Coxib available for intravenous or intramuscular injection. In trials of acute pain after orthopedic or oral surgery, parecoxib (20-40 mg) showed similar analgesic efficacy to that of ketorolac (30-60 mg), and superior efficacy to that of morphine (4 mg).(40,41)*When administered preoperatively, parecoxib (40 mg) has been demonstrated to be an effective analgesic agent compared with placebo.(30)*In cases of postoperative nausea and vomiting, or where the oral route for administration is inaccessible (eg, after oral-maxillofacial surgery), parecoxib may be an option to the few parenteral NSAIDs (eg, ketorolac [Toradol]) available for the treatment of moderate to severe postoperative pain.

CURRENT NSAIDS USE IN DENTISTRY:

Dentists commonly prescribe ibuprofen for the relief of mild to moderate acute dental pain or of postoperative dental pain and inflammation. NSAIDs may be prescribed for an extended period as an adjunct therapy for temporomandibular disorders with an inflammatory component, as well as for their analgesic effects.

DOSE AND EFFECTS OF NSAIDS :

Ibuprofen:

Moderate - analgesics: 200mg q6h.

High anti-inflammatory: 400-600mg q4h.

The extraction of impacted third molars has often been used as a model for testing the efficacy of new analgesics. Such surgeries usually involve acute, localized inflammation in young, healthy individuals in whom surgical removal of third molars is indicated. Pain intensity is of adequate severity to closely differentiate levels of analgesic efficacy.

Many dentists prefer codeine when some degree of sedation is desirable after difficult surgery. Opioids lack anti-inflammatory properties that may be beneficial, especially after extraction of impacted third molars.

GUIDELINES FOR USE OF SELECTIVE COX-2 IN DENTISTRY:

Few trials specific to dental pain have been carried out, although it appears likely that COX-2 inhibitors will become commonly used analgesic/anti-inflammatory agents in dental practice.

Prescription guidelines:

Drug: CELECOXIB

Indication: Analgesic; - 100-200mg/day.

Inflammation: Osteoarthritis :100-200mg/day.

Rheumatoid arthritis: 100-200mg/day upto BID.

Drug: ROFECOXIB

Indication: Analgesic: -12.5-25mg/dl.

Inflammation: osteoarthritis :- 12.5-25mg/dl.

Rheumatoid arthritis : 25-50mg/dl.

Warnings:

- Caution in patients with ASA/NSAID hypersensitivity and in patients with asthma.
- Caution in patients with pre-existing GI ulcer disease and intolerance.
- Caution in patients with liver and renal disease and urinary tract symptoms. • Caution in patients with fluid retention, hypertension, or heart failure. • Contraindicated in pregnant and breastfeeding women. • Contraindicated in patients on angiotensin-converting enzyme inhibitors. • Safety in children is not established.

III. CONCLUSION:

NSAIDs, despite their inherent side effects, are widely used drugs—both prescribed and as self-medication—because of their significant clinical spectrum and the relatively few complications with occasional use. As dental practitioners, we are encountering more patients on these medications and therefore need to consider the impact on the care we are providing. The breakthrough of selective COX-2 inhibitors with their significant decrease in acute GI complications will potentially lead to a change in the use of NSAIDs. An increase in the use of selective COX-2 inhibitors and a decrease in the use of the nonselective NSAIDs is expected. However, it is necessary to consider the potential effect of these medications in patients with past GI complaints. At present there are limited studies with COX-2 inhibitors in the dental models (eg, third molar extraction pain in healthy young patients). We know that GI complications from NSAIDs may occur by mechanisms other than COX inhibition (eg, direct irritation, alteration of mucosal blood flow independent of prostaglandin). Some studies demonstrate conflicting results, in which nonselective inhibition reduces markers of inflammation more effectively than do selective COX-2 inhibitors.(47). However, the present superior safety profile of COX-2 inhibitors should indicate their increased use over the next few years.

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