

# COX-2 Inhibitors in Dental Pain Management

## Inhibidores de la COX-2 en el Tratamiento del Dolor Dental

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DEL MURO, C. F. E.; GÓMEZ, C. K.; RODRÍGUEZ, G. N. A.; VARELA-PARGA, M.; LUENGO, F. J. A. & MEDRANO, R. J. C. COX-2 inhibitors in dental pain management. *Int. J. Odontostomat.*, 12(3):225-227, 2018.

**ABSTRACT:** Pain is a major symptom in many dental procedures. Studies show consistently that pain, including dental pain, is not effectively treated; management of pain is a critical and challenging component in dentistry. Improvement and efficacy on the treatment depends on knowing which treatments are the most effective. Knowing how well an analgesic works and its associated adverse effects is fundamental to clinical decision. The aim of this review is to provide information to the dentistry field on the treatment of dental pain specifically with COX-2 inhibitors providing a useful guide to dentist on controlling pain. Therefore, nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed analgesic agents in surgical outpatients. Major limitations of NSAIDs are their gastrointestinal (GI) adverse events (perforation, ulceration, and bleeding), impairment of hemostatic function, and renal failure (with long-term therapy). A new class of NSAIDs, COX-2 selective inhibitors (Coxibs), have been developed with the aim of reducing the GI adverse events of traditional NSAIDs while maintaining their effective anti-inflammatory and analgesic properties.

**KEY WORDS:** Pharmacology, cox-2 inhibitors, dental pain.

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### INTRODUCTION

Pain has been described as an emotional experience and sometimes subjective stimulation caused by harmfulness sensory nerve endings produced by damage, generally unpleasant, associated with tissue damage. It is the most common symptom for which patients see doctors. It appears if any tissue is injured and causes the subject to react by sometimes removing the stimulus, but damage has already taken place. Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. It has both sensory and an affective-motivational component. The nature and severity of pain is a consequence of both the sensory events arising from tissue damage, and the affective-cognitive mechanisms. A study has shown that anxiety and stress are correlated with the reported level of pain (Ong & Seymour, 2008).

**Dental pain.** Toothache and dental pain can originate from dental pulp or from periodontal ligaments. Dental pain is deep, somatic and presents a variety of central excitatory effects. Referred pain includes autonomic effects, induction of spasms and trigger points in

muscles innervated by the trigeminal nerve. It is described as a dull and oppressive feeling, sometimes throbbing, burning, intense and sometimes transitory. Often, the patient finds it difficult to identify the affected dental organ and can point to the pain as coming from other dental organ in one of the arcades or on face and neck; often dental pain is confused with other backgrounds (Rodríguez Reyes *et al.*, 2013).

Oral tissue injury activates the inflammatory process, which releases a large series of pain mediators. Mediators such as prostaglandins and bradykinins cause increased sensitivity and excitation of peripheral nociceptors, which usually have little spontaneous activity under normal conditions (peripheral sensitization). With repetitive C-fiber nociceptor stimulation from the periphery, excitatory amino acids such as glutamate and aspartate, as well as several peptides (including substance P) increase and cause activation of N-methyl-D-aspartate receptors of the postsynaptic second-order neuron in the dorsal horn. This leads to increased responsiveness of neurons in the central nervous system and to central

sensitization, which is responsible for the prolonged pain after dental surgery. Some of these mediators may be usefully inhibited or blocked by analgesics for example; the analgesic effect of non-steroidal anti-inflammatory drugs is primarily the result of their inhibition of the synthesis of prostaglandins and bradykinins through the inactivation of cyclooxygenase (Ong & Seymour).

**NSAID's Drugs.** All NSAIDs, including traditional nonselective drugs cyclooxygenase inhibitors-1 (COX-1) and subclass of selective cyclooxygenase-2 (COX-2) inhibitors, are a heterogeneous group of drugs. From the chemical point of view are organic acids that share certain therapeutic actions and adverse effects (Grosser *et al.*, 2011). Such drugs are the source of treatment of mild to moderate pain and its use is one of the bases suggested by the World Health Organization (WHO). The action of the NSAIDs are: antipyretic, anti-inflammatory and analgesic; however, these drugs, depending on their subclass, properties and structural chemical differences, as inhibition to COX (1 or 2) enzyme, determining its greater capacity within the above three properties. Even more, the particular interest on COX-2 which has the highest participation in the anti-inflammatory and analgesic capacity (Curlin, 2004; Daniels *et al.*, 2011).

However, peri-operative use of NSAIDs has been limited because of the associated gastrointestinal, coagulation, and renal side-effects. The selective COX-2 inhibitors (e.g. celecoxib, rofecoxib, valdecoxib, parecoxib, etoricoxib and lumiracoxib) are specifically designed to inhibit the COX-2 isoenzyme, which produces the prostaglandins; almost exclusively responsible for pain, inflammation and fever, without inhibiting the

constitutive COX-1. Even more, some studies suggest that selective COX-2 inhibitor reduce the incidence of gastro intestinal side effects compared with conventional NSAIDs (Chen *et al.*, 2004; Daniels *et al.*; Silva *et al.*, 2011).

Therefore, the aim of this review was to offer information to the dentistry field on the treatment of dental pain, specifically with COX-2 inhibitors, providing a useful guide to dentist on controlling different types of dental pain.

These type of drugs available on the market in Mexico, concerning to selective inhibitors of COX-2 are basically two: celecoxib and etoricoxib; and preferential to COX -2: meloxicam and nabumetone (Table I).

## CONCLUSION

It is of importance the pharmacotherapeutic management of dental pain, particularly of severe intensity pain, which is also accompanied by inflammation. COX-2 inhibitors are drugs that are poorly explored and implemented in the treatment of dental pain, mainly due to its controversy regarding cardiovascular-type adverse effects. However, In other studies (Nissen *et al.*, 2016) it was shown that despite the evidence of adverse cardiovascular outcomes in a placebo-controlled trial, resulting in the withdrawal of the selective COX-2 inhibitor rofecoxib in 2004. Therefore on the basis of a small number of events, the results of another trial suggested that

Table I. COX-2 inhibitors in dental pain management therapeutic guide.

| Drug                                    | Dental Indications   | Dosage  | Presentation  | Contraindications  |
|---|--|---|---|--|
| CELECOXIB<br>(celebrex)                 | Pain relief after complicated extraction or third molar surgery, post-surgical and alveolitis  | Initial dose: 400 mg in acute pain; maintenance dose of 100-200 mg per day                                | Capsules of 100 and 200 mg.<br>Box with 10, 20 and 30 capsules.                                       | Patients sensitive to the formula itself and even any other NSAIDs.<br>Asthmatic patients.   |
| ETORICOXIB<br>(Arcoxia)                 | Pain caused by mandibular or maxillary dislocation, post-surgical pain treatment and pulpitis. | Depending on the intensity of the pain goes from 60, 90 and up to 120 mg a day.                           | Coated tablets with 60, 90 and 120 mg.<br>Box with 7 and 14 tablets.                                  | Patients with hepatic dysfunction<br>Not to be used in patients with cardiovascular disease and patients sensitive to the formula itself or any other NSAID. |
| MELOXICAM<br>(Mobic, Dolocam, genérico) | Post-extraction tooth pain, mandibular and / or maxillary dislocation pain and alveolitis.     | Oral dose of 7.5 to 15 mg daily.<br>Parenteral 15 mg per day, oral follow-up not exceeding 15 mg per day. | 7.5 and 15 mg tablets.<br>Suspension of 7.5 mg in 5 mL.<br>Solution for injection IM 15 mg in 1.5 mL. | Hypersensitivity to the formula.<br>Do not administer in combination with other NSAIDs.<br>Patients with asthma.   |
| NABUMETONA<br>(Naburem)                 | Chronic pulpitis, post-extraction pain and alveolitis.   | Oral dose of 1g per day, being able to increase from 1.5 to 2 g per day.                                  | 500 and 750 mg tablets.   | Renal failure patients.<br>Do not combine with other NSAIDs or with methotrexate   |

cardiovascular harm may result from the use of higher-than-approved doses of celecoxib. Subsequently, the Food and Drug Administration (FDA) allowed continued marketing of celecoxib, but mandated a cardiovascular safety trial. In the Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen trial, they sought to assess cardiovascular, gastrointestinal, renal, and other outcomes with celecoxib as compared with two nonselective NSAIDs (Ahmed *et al.*, 2014). Otherwise, another study, concluded that both cox-2 inhibitor & non-steroidal anti-inflammatory drug improve post-operative complications after odontectomy of impacted lower third molar. Cox-2 inhibitor (celebrex) had superior analgesic efficacy when compared with the traditional NSAID (ibuprofen). Also, Cox-2 inhibitor (celebrex) reported insignificant improvement in edema and trismus than NSAID (ibuprofen) (Nissen *et al.*).

Thus, the present review proposes a therapeutic guide for the management of dental pain in specific situations indicating the management of these drugs, providing the dental community therapeutic tools for better treatments, as a result of avoiding errors in pharmacological prescription.

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**RESUMEN:** El dolor es un síntoma principal en muchos procedimientos dentales. Los estudios demuestran consistentemente que el dolor, incluido el dolor dental, no se trata de manera efectiva; el manejo del dolor es un componente crítico y desafiante en odontología. La mejora y la eficacia en el tratamiento depende de saber qué tratamientos son los más efectivos. Saber qué tan bien funciona un analgésico y sus efectos adversos asociados es fundamental para la decisión clínica. El objetivo de esta revisión es proporcionar información al campo de la odontología sobre el tratamiento del dolor dental específicamente con los inhibidores de la COX-2, proporcionando una guía útil para el control del dolor por parte del dentista. Por lo tanto, los fármacos antiinflamatorios no esteroideos (AINE) son los agentes analgésicos más comúnmente prescritos en pacientes ambulatorios quirúrgicos. Las principales limitaciones de los AINE son los eventos adversos gastrointestinales (perforación, ulceración y hemorragia), deterioro de la función hemostática e insuficiencia renal (con terapia a largo plazo). Una nueva clase de AINE, los inhibidores selectivos de la COX-2 (Coxibs), se han desarrollado con el objetivo de reducir los eventos adversos gastrointestinales de los AINE tradicionales mientras se mantienen sus propiedades antiinflamatorias y analgésicas efectivas.

**PALABRAS CLAVE:** Antiinflamatorios no esteroideos, Inhibidores selectivos de la COX-2, Tratamiento del dolor dental.

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Received: 03-04-2018

Accepted: 30-05-2018