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NSAIDS in Dentistry

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Introduction

NSAIDS are a class of medication that are used to treat pain, fever and other inflammatory process. This activity describes its history, mechanism of action, administration, adverse effects, indications, contraindications, classification etc. NSAIDS are more commonly employed for dental pain, because tissue injury and inflammation due to tooth abscess, caries, tooth extraction etc, is the major cause of acute dental pain. NSAIDS and antipyretics-analgesics are a class of drugs that have analgesic, antipyretics and anti-inflammatory action in different measures. In contrast to morphine, they do not depressed CNS, do not produce physical dependence, have no abuse liability and are particularly effect in inflammatory pain. They act primarily on peripheral pain mechanism but also in the CNS to raise pain threshold. Many analgesics of this class are' over the count'/ non-prescription drugs. (1)

NSAIDS should be "the first line analgesics" for acute post procedural dental pain, strategies to reduce the use of potentially addicting opoid analgesics and emerging research that may help predict an individual analgesic respond to NSAIDS before the surgical procedure.

Classification of NSAIDS

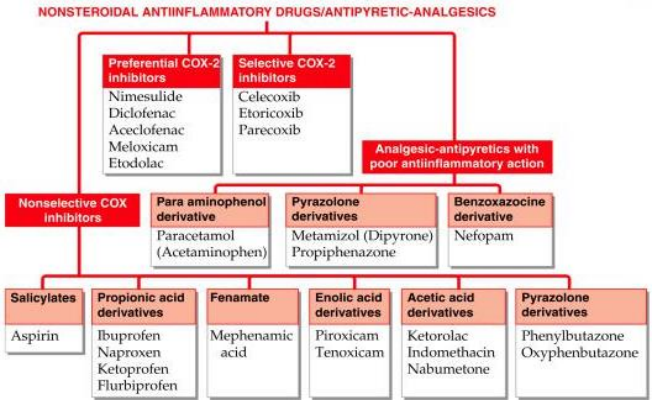


Chart 1: classification of NSAIDS (2)

COX -2 Inhibitors in Dental pain Management

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**.** (3) 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. (4)

NSAID´s Drugs

All NSAIDs, including traditional nonselective drugs cyclooxygenase inhibitors-1 (COX1) 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. (5) 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 is: 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. (6) However, peri-operative use of NSAIDs has been limited because of the associated gastrointestinal, coagulation, and renal side-effects. The selective COX2 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. (7) 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 types 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).

Drug	Dental Indications	Dosage	Presentation	Contraindications
CELECOXIB (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. Box with 10, 20 and 30 capsules.	Patients sensitive to the formula itself and even any other NSAIDs. Asthmatic patients.
ETORICOXIB (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. Box with 7 and 14 tablets.	Patients with hepatic dysfunction Not to be used in patients with cardiovascular disease and patients sensitive to the formula itself or any other NSAID.
MELOXICAM (Mobic, Dolocam, genérico)	Post-extraction tooth pain, mandibular and / or maxillary dislocation pain and alveolitis.	Oral dose of 7.5 to 15 mg daily. Parenteral 15 mg per day, oral follow-up not exceeding 15 mg per day.	7.5 and 15 mg tablets. Suspension of 7.5 mg in 5 mL. Solution for injection IM 15 mg in 1.5 mL.	Hypersensitivity to the formula. Do not administer in combination with other NSAIDs. Patients with asthma.
NABUMETONA (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. Do not combine with other NSAIDs or with methotrexate

Table 1: COX 2 in hibtor

Analgesics used in dentistry

Analgesics are considered one of the most important drugs groups in dental practice considering the prescription rate, clinical efficacy, cost-effectiveness and safety profile of this drug group. According to this level of importance in dental clinical practice, there are different approaches to develop treatment algorithm and guidelines for dental pain treatment in order to rationalize the use of analgesics. There is valuable evidence for significant relationship between nonrational use of analgesics and diminution of drug therapy, increased adverse drug reactions and socioeconomic consequences. (8,9) The prescription of analgesic drugs and treatment of dental pain is more complex when it is accompanied with other health disorders and diseases. In these cases, quantification of pain and its evaluation and treatment is a convoluted clinical challenge. The main complex challenges are patients with diabetes and other chronic diseases, patients with renal and hepatic insufficiency and patients with opioid addictive disorders. (10,11).

Moreover, Patients differ in their analgesic's response to different NSAIDS. If one NSAIDS is unsatisfactory in a patient, it does not mean other NSAIDS will also be unsatisfactory. Some subjects" feel better" on a particular drug, but not on a closely related one thus no single doe is superior to all others for every patient. In this context that availability of such a wide range of NSAIDS may be welcome. Some guidelines are:

1) Mild- to-moderate pain with little inflammation---Paracetamol or low dose Ibuprofen

2) Post extraction are similar acute but short-lasting pain---Ketorolac, a propionic acid derivative, diclofenac or nimesulide

3) Gastric intolerance to conventional NSAIDs are predisposed patient, etoricoxib or paracetamol.

4) Patient with history of asthma and anaphylactoid reaction to aspirin/other NSAID Nimesulide, cox-2 inhibitor.

5) Pediatric patients----only paracetamol, aspirin, ibuprofen and naproxen have been adequately evaluated in children should be preferred in them. Due to risk of Reye's syndrome, aspirin should be avoided unless viral infections can be ruled out.

6) Pregnancy --- paracetamol is the safest; low dose aspirin is probably the second best

7) Hypertensive, diabetic, ischaemic heart disease, epileptic and other patients receiving long term regular medication---possibility of drug interaction with NSAIDS should be considered and the physician consulted.

8) Patients with risk factors for cardiovascular diseases, stroke avoid etoricoxib, celecoxib; ibuprofen or low dose aspirin may be used. (12)

Factors influencing the analgesic selection

There are several factors that play a crucial role in the selection of analgesic drugs in dental pain treatment including:

1. Pathophysiological pain mechanism. This is a predictive factor in analgesic choice. Mechanisms include cancer metastases, postoperative dental pain, nerve root infiltration, nerve root infiltration, neuropathic

2. Patient age. The selection of analgesic is also determined by patient age. The administration of analgesics in children and elderly patients differs from adults' patients. The use of a number of analgesics in children is limited due to unmaturated metabolism processes. The elderly usually requires a restriction of analgesic dose due to decreased potential of metabolism and/or excretion with reflection in pharmacokinetics and pharmacodynamic of drugs.

3. Route of administration. This is determined by the general health condition of the patient, patient's characteristics of disease, bioavailability and pharmaceutical formulation of the analgesic. Oral use of analgesics is recommended where it is possible.

4. Patients-related features. There are several conditions, which may affect the success of analgesic treatment in dental patients. The placebo effect should be considered carefully by dental doctors. Initially, the dental doctors should address the potential renal and hepatic toxic effect, including the gastrointestinal disturbances which may impact the pharmacokinetic and safety profile. (13).

Types of pain in dentistry	Analgesic drug	Dosing	Adverse effects
Acute dental pain	Ibuprofen Ketoprofen Diclofenac Flurbiprofen Naproxen Sodium Acetaminophen Celecoxib Codeine/Acetaminophen	200–400 mg every 6–8 h 25–75 mg tbl every 6–8 h 50 mg tbl. 3 times daily 50–100 mg tab every 8 h 500 mg, followed by 250 mg every 6–8 h 500–1000 mg 3 times daily 200 mg 2 times daily 30–60/325–650 mg every 4–6 h	Gastric ulceration-bleeding, diarrhea, hepatotoxicity, allergy, skin rashes, urticaria, cardiovascular-MI, atherothrombosis, CHF, ischemic stroke; Opioid side effects-respiratory depression, dependence, etc.
Postoperative pain	Ibuprofen	200–400 mg every 6–8 h	NSAIDs associated side effects,

Periodontal surgery Orthodontic tooth movement Pain from pulpal or periapical tissue.	Ibuprofen/Acetaminophen Naproxen	(OTC)400/1000 mg every 6–8 h220 mg every 12 h (OTC)	however, OTC doses are better tolerated.
Dental surgery—impacted third molar surgery and Dental surgery—dental root canal treatment	Diclofenac/Paracetamol Ibuprofen/Paracetamol	100/1000 mg single oral dose with 8 h observation 600/1000 mg 30 minutes before procedure or after surgery	Nausea, drowsiness headache
After third molar extraction Oral surgical or endodontic treatment Temporomandibular disorders Nontraumatic dental Conditions with severe pain.	Hydrocodone codone Codeine Tramadol	10 mg every 4–6 h 5 mg every 6 h 60 mg every 6 h 50–75 mg 4–6 h.	Nausea, sedation, dizziness, constipation, addiction, sleep disorders.
Intensive dental pain	Oxycodone/Ibuprofen Oxycodone/Acetaminophen Hydrocodone/Acetaminophen	5/400 mg every 6 h 5/500 mg every 6 h 5/325 mg or 7.5/500 mg every 4–6 h	Nausea, sedation, dizziness, constipation, addiction, sleep disorders.

Table 2: General use of analgesic drugs in the different types of pain in dentistry.

Mechanism of post-surgical dental pain and its relationship to analgesic efficacy

Dental postsurgical pain is mainly driven by in Flammarion, with cyclooxygenase - derived prostaglandins being key sensitizers of free nerve ending to other mediators of pain such as histamine, bradykinin, adenosine triphosphate (ATP), and low Ph. (14)

These free nerve endings also express other receptors such as transient receptor potential vallinoid (TRPV) ion channels, voltage-gated sodium (Nav) and calcium (VGCC) channels, and acid-sensing ion channels (ASICs) besides those specific for sensitizing or pain-provoking mediators. Activation of these receptors generates action potentials that travel along thinly myelinated A delta or unmyelinated C fibers, which make synaptic connections to second-order neurons in the dorsal horn of the spinal cord.

Chemicals released from the central terminals of free nerve endings include substance P and the excitatory amino acid glutamate, which cause the second-order neurons to depolarize and generate their own action potentials. (15) Eventually, synaptic connections with supraspinal third-order and fourth-order neurons that reside in the thalamus, hippocampus, and cerebral cortex result in the physiologic aspects and emotional components of the pain response.

While the surgical trauma of third molar removal involves both soft tissue and bone, the wound surface is

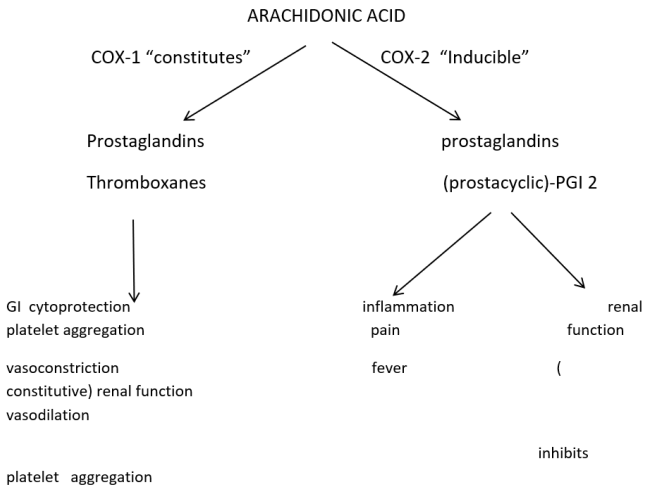
relatively small compared to other medical surgical procedures. However, a marked increase in prostaglandins can be measured both locally (16) and systemically.

The generation of prostaglandins and other pain-sensitizing or pain-provoking mediators in the central nervous system (CNS) also augments pain transmission (17).

Since traditional NSAIDs block both cyclooxygenase isoforms (COX-1 and COX-2) and the ultimate generation of prostaglandins (18).

The remarkable efficacy and safety of currently marketed NSAIDs from a mechanistic standpoint in treating postsurgical dental pain should not be surprising. Some physiologic roles of cyclooxygenase (COX) isoforms and their products.

Note the opposing cardiovascular effects of COX-1 and COX-2 products. Ketorolac, being 300-fold more selective for blocking COX-1, has a higher potential than other nonsteroidal anti-in flammatory drugs (NSAIDs) of inducing gastrointestinal (GI) bleeding and ulceration. Celecoxib, by being 8-fold selective for blocking COX-2, produces less GI toxicity but greater cardiovascular risk than other NSAIDs (19).



Acetaminophen is a relatively weak inhibitor of both cyclooxygenase enzymes that, unlike ibuprofen, naproxen, or diclofenac, does not block the substrate binding channel of the enzymes but disrupts electron transfer within the catalytic center (21). This feature may allow acetaminophen to work more downstream than traditional NSAIDs in the arachidonic acid / cyclooxygenase cascade. It is this mechanistic difference in biochemical inhibition of the cyclooxygenase enzyme that provides the rationale for combining ibuprofen with acetaminophen to produce a synergistic effect (21). There may also be additional central mechanisms contributing to the actions of this drug, including the activation of cannabinoid or descending serotonergic systems (22).

Analgesic combination

Combination of aspirin and paracetamol is addictive (not supra-addictive) and a ceiling analgesic effect is obtained when the total amount of aspirin+ paracetamol is ~1000mg. The same is true of combination are superior to single agents either in efficacy or in safety. It at all used, such combination should be limited to short period.

Combination of codiene (an opioid analgesic) with aspirin or paracetamol is also addictive, but in this case combination provides additional analgesia beyond the ceiling effect of aspirin/paracetamol, provides each is given at its full dose, which will produce opioid side effects as well. The mechanism of pain relief by these two classes of drugs are different. Such combination should be considered only for pain refractory to a single agent (23).

Indications of NSAIDS

- NSAIDS are a drug class FDA approved for use has antipyretic, anti-inflammatory and anti-analgesic agents (24). These effects NSAIDS useful for treating muscle

pain, dysmenorrhea, arthritic condition, pyrexia, gout, migraine and used as opoid sparing agents in certain acute trauma cases (25,26,27).

- Topical NSAIDS (diclofenac gel) are also available for use in acute tenosynovitis, ankle sprains and soft tissue injury (28,29,30,31).

Adverse effects of NSAIDS

- Gastrointestinal: Nausea, anorexia, gastric irritation, erosion, peptic ulceration, gastric bleeding/perforation, esophagitis.
- Renal: Sodium and water retention, chronic renal failure, nephropathy, papillary necrosis(rare).
- CVS: Rise in BP, risk of myocardial infarction (especially with COX-2 inhibitor)
- Hepatic: Raised transaminases, hepatic failure (rare).
- CNS: Headache, mental confusion, vertigo, behavioural disturbances, seizures precipitation
- Haematological: Bleeding, thrombocytopenia, haemolytic anemia and agranulocytosis.
- Others: Asthma, exacerbation, nasal polyposis, skin rashes, pruritus, angioedema (32).

Contraindications

According to the package insert, NSAIDs are contraindicated in patients:

1. With NSAID hypersensitivity or salicylate hypersensitivity, as well as in patients who have experienced an allergic reaction (urticaria, asthma, etc.) after taking NSAIDs
2. Who have undergone coronary artery bypass graft surgery?
3. During the third trimester of pregnancy.

Drug interaction with NSAIDS

Drug interactions with NSAIDs

Pharmacodynamic		Pharmacokinetic	
Diuretics	: ↓diuresis	Oral anticoagulants	Metabolism inhibited; Competition for plasma protein binding
β blocker	: ↓antihypertensive effect	Sulfonylureas	
ACE inhibitors	: ↓antihypertensive effect	Phenytoin	
Anticoagulants	: ↑risk of g.i. bleed	Valproate	
Sulfonylureas	: ↑risk of hypoglycaemia		
Alcohol	: ↑risk of g.i. bleed	Digoxin	↓Renal excretion of interacting drug
Cyclosporine	: ↑nephrotoxicity	Lithium	
Corticosteroids	: ↑risk of g.i. bleed	Aminoglycosides	
Selective serotonin reuptake inhibitors	: ↑risk of g.i. bleed	Methotrexate	

Table 3: drug interaction withs NSAIDs (33).

Summary

Nonsteroidal anti-inflammatory drugs (NSAIDs), including both the traditional nonselective NSAIDs and the selective cyclooxygenase (COX)-2 inhibitors, are widely used for their anti-inflammatory and analgesic effects. They are routinely prescribed in dental practice for the management of pain and swelling. Their use in treating acute dental pain and chronic orofacial pain, as adjuncts to the treatment of periodontal disease, and to minimize edema following surgical procedures is well documented. However, long-term utilization of nonselective NSAIDs could increase the risk of gastrointestinal symptoms, ranging from mild (e.g., dyspepsia, nausea, or vomiting) to serious gastric problems (e.g., gastric bleeding or perforation). Therefore, selective COX-2 inhibitors have been developed with fewer GI side effects but the recently identified cardiovascular adverse reactions limit their routine use in dental practice. Another major concern for oral physicians is NSAID-induced mucosal lesions and prolongation of bleeding time during invasive dental procedures. This article reviews therapeutic and analgesic uses of NSAIDs in dentistry. The various

issues surrounding NSAID-induced adverse reactions and their implications in dentistry are also discussed.

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