

A Review of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Medications in Dentistry: Uses and Side Effects

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ABSTRACT

Introduction: Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) are the most commonly used as anti-inflammatory drugs because of their ability to cope with aches and pains. Consideration of rational selection of NSAIDs and a basic understanding of the pharmacokinetic and pharmacodynamic features is important. The dentist must assess the risks and benefits of each drug by considering the medical history needs of everyone. Medications must be prescribed in the appropriate dosage to reduce or avoid complications related to NSAIDs.

Objective: To review the uses nonsteroidal anti-inflammatory drugs (NSAIDs) in dentistry.

Methods: Scientific evidence and clinical cases were drawn from the literature to support this review and information about the use of anti-inflammatory nosteroids in dentistry was collected.

Discussion: The use of NSAIDs in dentistry can be done both before the action and after the action. The administration of NSAIDs is based on doses of various NSAIDs. Each type of NSAIDs has advantages for

its beneficial actions and side effects.

Conclusion: The literature review proves that the use of NSAIDs in the field of dentistry is very broad. Each drug has side effects and work power, each of which is tailored to the needs and systemic conditions of patients who require administration of this drug. The accuracy of the use or administration of NSAIDs is supported by the knowledge and expertise of doctors or dentists.

Keywords: NSAIDs, Dosages, Side effect

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INTRODUCTION

In practice, dentists always deal with complaints of pain or pain in patients with simple analgesic drugs, and in fact have not been able to control pain due to inflammation. One way to deal with pain is the administration of analgesic drugs. Drugs that are often used in pediatric patients include nonsteroidal anti-inflammatory drugs (NSAIDs). It works pharmacologically to inhibit the prostaglandin and be able to reduce pain, fever with inflammation and that is accompanied by other pain disorders.¹

The use of NSAIDs is very effective for reducing pain symptomatically, most widely prescribed and are the first choice in the treatment of inflammatory pain. There are various types of NSAIDs that are known, such as aspirin, paracetamol, ibuprofen, mefenamic acid, indomethacin, diclofenac, piroxicam and nimesulide. From various kinds of NSAIDs, each has advantages and disadvantages that are seen in the therapeutic effect and the side effects caused. Therapeutic effects related to the mechanism of action of this preparation. The use of NSAIDs in children really needs attention.¹

Consideration of the selection of NSAIDs in children is certainly based on the results of research experts who have been tested for safety. The important things to consider is the rational administration of drugs and a basic understanding of the pharmacokinetic and pharmacodynamic features of the drug. Pharmacokinetics is a pharmacological aspect that includes the fate of drugs in the body, including drug absorption, distribution, metabolism, and excretion. Where gastric acidity is lower in children than in adults can affect the

absorption of certain drugs, as well as a slower gastric emptying time in children can also affect the rate of drug absorption.^{1,2}

In the process of drug metabolism, it tends to be slower in neonates and increase progressively over several months of life, and will exceed the speed of adults in several years of life. This affects the half-life of drugs which can be shorter due to increased metabolic rate. For pharmacodynamics concerning the mechanism of action of pharmacological agents, where in immature individuals can change, among others, due to the reduction or increase in the number of receptors on which the drug works (hormone neurotransmitters) and the immaturity of the structural and functional metabolic immaturity of the receptors.^{2,3}

Broadly speaking, NSAIDs are classified into aspirin and nonaspirin NSAIDs. In addition, in 2016, the ADA Delegation House adopted a statement that said, "Dentists should consider nonsteroidal anti-inflammatory analgesics as a first-line therapy for the management of acute pain".⁴ Medications must be prescribed in the appropriate dosage and duration to reduce or avoid complications associated with NSAIDs.⁵

METHODS

Scientific evidence and clinical cases are drawn from the literature to support this review and information on the use of NSAIDs in pediatric dental care is collected.

LITERATURE SEARCH

A review was carried out looking for about the use of NSAIDs in pediatric dental care. On April 30th, 2020, a literature search was performed using the following keywords: "Anti-

inflammatory in dentist, NSAIDs in pediatric dentist, anti-inflammatory drugs used in pediatric dentists." The following databases were searched: PubMed, GoogleScholar, and Science Direct.

DISCUSSION

1. Types of NSAIDs in Dentistry

Table of NSAIDs used in dentistry^{6,7}

Drug Substance		Drug Dosage Form	Dose of Adult	Dose of Children
Acetylsalicylic acid	GDP, aspirin	Tablet	500 mg/4-6 hours	-
Dexketoprofen thrometamol	Enantyum, Kettesse	Tablet Solution Injection	50 mg/8-12 hours intramuscular or intravena	Not recommended
Diclofenac	GDP, Voltaren	Tablet	75 mg/24 hours intramuscular	Not recommended
Ibuprofen	GDP, Dalsy, Espidifen, Neubrufen	Tablet Oral Suspension Injection	400-600 mg/6-8 hours	20 mg/kg/days 3-4 doses
Ketorolac thrometamol	Droal, Toradol, Tonum	Tablet Solution Injection	20 mg initial dose + 10-30 mg/4-6 hours intramuscular or intravena	Not recommended for children under 16 years
Naproxen	GDP, Naprosyn, Antalgin 550	Tablet, Suppositories	250 -500 mg/12 hours	10 mg/kg/days 2 doses
Piroxicam	GDP, Feldene, Improntal	Tablet, Suppositories	40 mg/day on the first day 20 mg/day the following day	Not recommended
Celecoxib	Celebrex	Capsules	200 mg/12-24 hours	Not evaluated in children

Other literature according to Bailey et al suggests that ibuprofen is conventionally considered a prototype of a large group of synthetic compounds known efficacy for anti-inflammatory, analgesics, and antipyretics. This therapeutic effect and its most prominent side effects can occur explained almost entirely by their ability to inhibit cyclooxygenase (COX) required for the synthesis of various prostanoid families.^{8,9,10}

Studies report that COX-2 selective use of NSAIDs increases the risk of non-fatal myocardial infarction (MI) without substantial effects on fatal events. This was also confirmed to be the case with all other NSAIDs, including naproxen, in a recent systematic review. Rofecoxib was in 2004 a statistically increase. This can be elaborated by an imbalance between hemostatic prostanoids, namely prostacyclin and TXA₂, which is induced by selective inhibition of prostacyclin-dependent COX-2 production while maintaining a sustainable COX -1-dependent TXA₂ production by platelets.¹¹

2. Pathomechanism of NSAIDs

NSAIDs are very heterogeneous chemical structure, where side effects and therapeutic effects are related to the similarity of the mechanism of action of these preparations on the enzyme cyclooxygenase (COX). The mechanism of action associated with PG biosynthesis began to be reported in 1971 by Vane and colleagues who showed invitro that low doses of aspirin and indometasone inhibited PG enzymatic production. It has also been proven that if a cell is damaged the PG will be released.^{12,13,14}

However, NSAIDs do not generally inhibit the biosynthesis of leukotrin, which is known to play a role in inflammation. Each drug inhibits cyclooxygenase in a different way. NSAIDs are grouped according to chemical structure, acidity and initial availability. And now those who are tolerated are grouped based on their selectivity inhibition in the discovery of two forms of the enzyme constitutive. COX-1 always exists various body tissues. But will increase in an inflammatory or pathological state. So that this enzyme becomes dysfunctional and unable to convert arachidonic acid into a mediator of prostaglandin inflammation.^{13,14}

NSAIDs that are not selectively inhibiting COX-1 and COX-2 are ibuprofen, indomethacin and naproxen. Acetosal and ketorolac are very selective in inhibiting COX-1. Piroxicam is more selective in blocking COX-1, while those that are selective in blocking COX-2 include diclofenac, meloxicam, and nimesulid. Celecoxib and rofecoxib are very selective in inhibiting COX-2.¹⁵

NSAIDs also increase levels of endocannabinoid N-arachidonylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG), which are metabolized by COX-2. AEA and 2-AG exert analgesic, anti-inflammatory, and anxiolytic effects through activation of cannabinoid receptors or through direct interaction with ion channels involved in sensing, so that the analgesic effect of NSAIDs can be mediated in part through potentiation of endocannabinoid signaling. Omega-3 fatty acids and their epoxide metabolites also have anti-inflammatory and anti-nociceptive effects.^{16,17,18}

3. Uses of NSAIDs in Dentistry

No.	Authors and Titles	Years	Conclusion
1.	Fajriani Provision of Nonsteroidal anti-inflammatory drugs in children Journal: Indonesian Journal Paediatric 2008; 15 (3): 200-204	2008	NSAIDs can reduce pain symptomatically, the most widespread of drugs prescribed worldwide and become the first choice drug for inflammatory pain. There are many types of NSAIDs that we have, such as aspirin, paracetamol, ibuprofen, mefenamic acid, endomethacin, diclofenac, piroxicam and nimesulide. Each type of NSAID has advantages and disadvantages for its beneficial actions and side effects. Actions that are beneficial and detrimental to the effects of NSAIDs can be related to the mechanism of action. Using NSAIDs for children must be considered.
2.	Gholamreza S, et al. Dentists' Prescription Patterns of Non-Steroidal Anti-inflammatory Drugs and Antibiotics: A Systematic Review Journal: Journal of Clinical and Diagnostic Research. 2018 Mar, Vol-12(3): FE04-FE09	2018	The results show different prescription patterns of NSAIDs and antibacterial drugs by dentists in various countries; however, amoxicillin and amoxicillin/clavulanic acid, metronidazole, and macrolide are the most commonly prescribed antibacterial drugs and ibuprofen as the most frequently NSAIDs used by dentists.
3.	SachinK, Samuel T, Himanshu A. Evaluating the effectiveness of nonsteroidal anti-inflammatory drugs for relief of pain associated with temporomandibular joint disorder: A systemic review Journal: ClinExp Dent Res. 2020;6:134–146	2020	In this systematic review, there is heterogeneity in the type of intervention, NSAID dosage used, control used, duration of study, and diagnosis of TMD being treated. The earliest studies included were published in 1996, and there is evidence to suggest that NSAIDs have been further investigated, with those focused on reducing side effects, especially GI and cardiovascular.
4.	Datta R , Yasmin G, Jaspreet SB, Amandeep S. A survey of analgesic and anti-inflammatory drug prescription for oral implant surgery Journal: PlastAesthet Res Vol 2 Issue 2	2015	The study was conducted to determine which analgesic and anti-inflammatory drugs are preferably prescribed by oral implantologists in India by gathering information about their prescription habits for analgesics and anti-inflammatory drugs. Data analysis showed that the majority of dentists (85.8%, n = 285) prescribed conventional non-steroidal anti-inflammatory drugs (NSAIDs) for implant surgery.
5.	AnushaE, Mustafa T, HoussamA and Wang HL Effect Of NSAID on Periodontal and dental implant therapy Journal: Compendium Volume 40, Issue 2	2019	Identified articles evaluating the effect of NSAIDs administration on outcomes after periodontal treatment (nine clinical studies) and placement of dental implants (four studies in animals and two clinical studies in humans). Conflicting results were found in the effects of NSAIDs during periodontal wound healing. Administration of NSAIDs, especially COX-2 inhibitors can selectively inhibit bone formation around orthopedic implants.

In connection with the literature conducted by Theken et al, regarding studies in Australia post acute surgical pain after extraction of the third molar have shown that, although NSAIDs are very effective on average, 20-30% of patients need opioid salvage drugs within 4-6 hours of dose. Initial NSAIDs, indicate these are individuals where NSAIDs fail to provide adequate pain relief throughout the dosing interval.^{19,20, 21, 22, 23}

In the second study, conducted by Elisabeth et al, there was insufficient data to recommend NSAIDs, the number of doses, or dosage intervals that most effectively reduced postoperative endodontic pain.^{24,25,26,27} NSAIDs, acetaminophen, and opioids are the main drugs used for medical management of dental pain and the combination of opioid and non-opioid analgesics shows additive effects on pain management, because they produce analgesia by different mechanisms. The combination of ibuprofen and acetaminophen with codeine for 3-7 days is the most common form of prescription to reduce tooth pain, though, some clinicians use a combination of tramadol and acetaminophen in the management of acute postoperative tooth pain.²⁸

In the sixth study conducted by Sachin K, Samuel T, Himanshu A in 2020, the inclusion criteria in this study were randomized controlled trials in humans, published in the last 50 years evaluating the effects of NSAIDs on TMD.²⁸

In the previous literature related to researchers conducted by Anusa E, et al regarding the effects of the use of NSAIDs on periodontal and dental implant treatment. In this literature, the authors have highlighted available evidence regarding this effect from experimental studies in laboratory animals and human clinical studies. Conflicting results from animal models can be related to the species studied, the methodology used, and the pharmacokinetics of the drug which can be influenced by local or systemic compensation factors.^{25,27,29} Further research is needed to assess the effects of NSAIDs for a short period of simulating postoperative use. Findings from the medical literature indicate that administration of systemic NSAIDs during the healing period after implant placement interferes with bone healing. But findings from experimental periodontitis and human periodontitis models show that NSAIDs can slow the rate of alveolar bone loss or produce no effect at all. This is an interesting major problem to find out the effect of systemic administration of NSAIDs on bone healing and osseointegration after placement of dental implants.²⁶

Two systematic reviews have been carried out to review the literature on the possible influence of NSAIDs on osseointegration of titanium implants. The first review was conducted by Gomes et al. concluded that osseointegration was disrupted by the presence of conventional NSAIDs, while a review was carried out by Kalyvas et al. concluded that short-term postoperative NSAIDs did not appear to have a negative impact on osseointegration.²⁶

4. Side Effects of NSAIDs

Colberg et al in 1996 suggested that between diclofenac and meloxicam there was no difference in terms of anti-inflammatory analgesic properties, whether administered orally or by injection. Comparative studies conducted show

pain, heat and inflammation on administration of nimesulide 200 mg/day peroral or 400 mg/day per rectal equal or better than seaperase (15 mg), flurbiprofen (300 mg), diclofenak (150 mg), naproxen (150 mg) 1000 mg), fiprazone, piroxicam, mefenamic acid in patients with inflammation of the ears, nose, throat, cancer pain, gynecological disorders, urogenital abnormalities, acute musculoskeletal injuries, thrombophlebitis, back pain, tendonitis and post-operative diseases and post surgical procedures.^{1,15}

a. Gastrointestinal changes

The relationship between gastroduodenal mucosal injury and NSAIDs is well known. PGs modulate almost every aspect of mucosal defense, and this is evident from the increased susceptibility of the GI mucosa to injury after the use of chronic NSAIDs. Studies have shown that the proportional significance of patients experiencing symptoms of upper GI, usually dyspepsia, and lesions ranging from petechial bleeding to gastric ulcer bleeding, as seen on endoscopy.

b. Cardiovascular side effects

Safety of NSAIDs is a very controversial topic because previous studies have shown an increased risk of CV with all nonselective NSAIDs and selective COX-2 inhibitors except naproxen (1000 mg daily) and low-dose ibuprofen (1200 mg daily). Clinical trials have found that ibuprofen and naproxen can weaken the antiplatelet effect of low-dose aspirin, which is used for the prevention of myocardial infarction and other CV diseases.

c. Hepatotoxicity

Nonselective NSAIDs, such as diclofenac, sulindac, and aspirin, have been reported to be more commonly associated with hepatotoxicity. Hepatotoxicity which is used in antiplatelet indications. Newer COX-2 selective inhibitors (eg, Celecoxib, nimesulide) are also associated with hepatotoxicity. Although celecoxib is said to have a lower potential for hepatotoxicity.

d. Kidney effects and hypertension

Using of NSAIDs routinely increases the risk of kidney disorders. Decreased acute kidney function occurs in 0.5% to 1% of patients who regularly consume NSAIDs. Pathogenesis is believed to be renal vasoconstriction secondary to dilated PG inhibition, thereby increasing peripheral resistance and blood pressure. COX-2 expression has also been found to be regulated in salt depletion status in renal ischemia.

e. Dermatological side effects

NSAIDs are one of the most commonly prescribed drugs in medical practice because of their ability to inhibit lipooxygenase (LOX) and COX pathways. Chronic use of NSAIDs has been found to produce various adverse skin reactions

Long-term use of NSAIDs can produce hyperkalemia, sodium and water retention, hypertension and CRF. In patients who are healthy and well hydrated, short-term treatment with NSAIDs is not clinically dangerous, but treatment in patients with existing kidney disease can cause increased nephrotoxicity.¹⁸

Side effects are increased in the presence of comorbidities and in polypharmacy patients. The action of ACEI hypertension, diuretics and β blockers can be reduced if NSAIDs are used for more than 5 days. NSAIDs should be avoided in patients using lithium, methotrexate and digoxin to increase plasma levels of this drug which cause toxicity.^{29,30}

NSAIDs inhibit renal lithium excretion and can cause lithium to accumulate to toxic levels, potentially leading to kidneys, gastrointestinal, and central nerve toxicity. Both ibuprofen 1800 mg/day and 750 mg naproxen/day for 6 days have been shown to increase previously stable plasma lithium levels, and the magnitude of this effect varies greatly between individuals.^{31,32}

Because there is an induction of COX-2 at the site of inflammation, it is believed that the therapeutic properties of NSAIDs are mainly for inhibition of COX-2. NSAIDs, however, have adverse side effects that limit their use in patients with gastrointestinal (GI) ulcers, asthma, anticoagulant therapy patients or with kidney/liver disease, or pregnant women.^{21,33,34}

CONCLUSION

Various medical therapies using NSAIDs are often prescribed by dentists. Literature review proves that the use of NSAIDs in the field of dentistry is very broad. Various studies have been conducted to determine safest type of medicine. However, each drug has side effects and work power, each of which is adjusted to the needs and systemic conditions of patients who require administration of this drug. The accuracy of the use or administration of NSAIDs is supported by the knowledge and expertise of doctors or dentists.

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