

Current Concepts of Analgesics in Dental Pain Management

Monika Kaushik*, Atul Kaushik**

Abstract

Pain is the most important symptom that brings the patient to the dentist. Analgesics are the drugs which relieve pain as a symptom, without affecting its cause. Analgesics most commonly prescribed in dentistry for pain relief include the non steroidal anti-inflammatory drugs (NSAIDs) and various opioid-containing analgesic combinations. Selection of an analgesic for the management of dental pain should be judiciously planned. When prescribing an analgesic, the dentist should advise the patient to take the initial dose as soon as feasible and then follow a fixed dosing schedule for at least the expected duration of the most intense pain. In all cases, however, the primary analgesic should be taken on a fixed schedule, not on a "pro re nata" (prn) basis, which only guarantees the patient will experience pain. This paper summarizes the currently available oral analgesics and their appropriate usage for pain relief in dentistry.

Keywords: Dental pain management; Analgesics; Prostaglandin; Endogenous opioids receptors, Fixed dosing schedule.

Introduction

The first "prescription" for pain management can be traced 2,400 years back, when Hippocrates suggested juices of willow bark to alleviate the pain of childbirth. Salicylic acid was obtained by hydrolysis of the bitter glycoside obtained from this plant. Sodium salicylate was used for fever and pain in 1875 and led to the introduction of acetyl salicylic acid (Aspirin) in 1899, which remains one of the most common remedies for pain till date. Opioid use has been known from the earliest times. Serturmer isolated the active principle of opium (morphine) in 1806 and gave clinicians for the first time a chemically pure, highly effective analgesic.¹ Continued advances in the development of aspirin-like and morphine-like drugs have made available a broad spectrum of agents to manage dental

pain. The selection of a drug should be judiciously based on several important factors like actual or expected intensity of pain, patient's medical history, drug's pharmacologic profile and the ease and cost of obtaining the medication.

Managing both acute and chronic pain is inherent to dental practice. Numerous analgesics are currently available and the recent introduction of new agents provides even more options from which to choose. The aim of the present article is to provide a brief review of the drugs that should be considered for the management of pain in dental practice.

Analgesics in dental pain management

No simple definition of the word *pain* can be acceptable to all. Rapid developments and discoveries in the field of pain research will mandate periodic updating and redefinition. Currently pain can be defined as "An unpleasant emotional experience usually initiated by a noxious stimulus and transmitted over a specialized neural network to the central nervous system where it is interpreted as such".² Pain is a warning signal and is the most important symptom that brings the patient to the dentist. Pain can be separated into two broad categories: acute and

Author's Affiliation: *Consultant Implantologist, No.46, 6th Cross, AECS lay Out, Ashrama Colony, Sanjay Nagar, Bangalore-560094, Karnataka, India. **Senior Lecturer, Dept of Oral Medicine and Radiology, SGT Dental College and Hospital, Budhera, Gurgaon.

Reprints Requests: Dr. Monika Kaushik, Consultant Implantologist, No. 46, 6th Cross, AECS lay Out, Ashrama Colony, Sanjay Nagar, Bangalore-560094, Karnataka, India.

E-mail: drmonikakaushik@gmail.com

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chronic.³ Acute pain may be of short duration, unbearable and associated with other effects such as heightened arousal, tachycardia, tachypnea and anxiety. In contrast, chronic pain typically lasts from months to years. The body has become adapted to this level of pain and often there is no increased sympathetic response.

Analgesics are "the drugs that selectively relieve pain by acting in the central nervous system (CNS) or on peripheral pain mechanism, without significantly altering consciousness". These are divided into two groups: Non opioid / aspirin like / NSAIDs analgesics and Opioid / narcotic / morphine like analgesics.¹

NSAIDs and Prostaglandin (PG) Synthesis Inhibition

Tissue damage stimulates the release of various inflammatory mediators such as PG, kinins, leukotrienes, substance P and histamine at the site of injury. These mediators initiate and magnify nociceptive impulses that are transmitted to the CNS for the perception of pain.⁴ PG are especially important in sensitizing peripheral neurons and are also synthesized in the spinal cord and possibly higher brain centers to enhance pain sensitivity by recruiting additional secondary neurons.

Aspirin and related NSAIDs work at the site of tissue damage, spinal cord and higher brain centers to block PG generation, which is considered to be their major mechanism of action. PG, prostacyclins (PGI₂) and thromboxane A₂ (TXA₂) are produced from arachidonic acid by the enzyme cyclooxygenase (COX), which exists in a constitutive (COX-1) and an inducible (COX-2) isoforms. COX-1 serves physiological "house-keeping" functions such as hemostasis, stomach mucosal integrity and regulation of normal renal blood flow. COX-2 is a largely inducible form whose synthesis is activated in damaged or stimulated tissues and leads to the formation of pro-inflammatory PG. COX-2 plays a major role in inflammation, pain and fever.⁵ A new COX-3 has been described that is produced by the same gene that encodes

COX-1. This COX-3 is found in the brain and is inhibited by clinically achievable concentrations of acetaminophen.⁶

Role of Endogenous Opioids Receptors

Opioid analgesics exert their actions by interacting with specific receptors present on neurons in the CNS and in the peripheral tissues. Radioligand binding studies have divided these receptors into three types - μ (mu), κ (kappa) and δ (delta). Endogenous opioid peptides also play a pivotal role in blunting pain.⁷

Morphine and related opioid analgesics exert most of their pharmacologic effects by stimulating the μ opioid receptor. In addition to analgesia, it can cause euphoria, nausea, vomiting, miosis and constipation. In overdose, respiratory depression is the primary concern; chronic use can lead to physical and psychological dependence.

Nalorphine and related opioid agonist-antagonists promote analgesia by stimulating the δ opioid receptor. Analgesic and respiratory depressant effects are similar to those elicited by morphine. Sedation is a common side effect and these are more likely to produce dysphoria than euphoria. Physical dependence is less problematic with δ agonists.¹

NSAIDs

As the prototypical of NSAIDs, aspirin remains a standard against which other orally active analgesics are compared. It is rapidly converted in the body to salicylic acid which is responsible for most of its actions. It is relatively selective for COX-1 and is therefore prone to causing gastric bleeding and ulceration, especially with high doses and chronic use. Aspirin inhibits COX-1 irreversibly by acetylating it and return of COX activity depends on synthesis of fresh enzyme. Typical doses of 325 to 650 mg encompass most of aspirin's analgesic dose-response curve in the average adult.

Ibuprofen was the first member of propionic acid derivatives group to be introduced as a

better tolerated alternative to aspirin. Some studies demonstrate it having analgesic properties superior to aspirin. A 400 mg dose of ibuprofen has been shown to have a greater peak analgesic effect and a longer duration than 600 to 1,000 mg of aspirin.⁸ The principal effect of prescribing doses of ibuprofen larger than 400 mg for pain relief is that the duration of maximum analgesia is prolonged.⁹ Naproxen, an NSAIDs structurally related to ibuprofen, is probably more efficacious and better tolerated in anti-inflammatory doses. It is longer acting and has the advantage of twice daily dosing. A 220 mg dose of naproxen sodium is equivalent to 200 mg of ibuprofen in analgesic onset and peak effect but has a longer duration of action.¹⁰ Diclofenac Sodium is a newer NSAIDs, similar in efficacy to naproxen. It has a good tissue penetrability and concentration in synovial fluid is maintained three times longer time than plasma, exerting extended therapeutic effect in joints. A 50 mg dose provides quick relief in post-traumatic and post-operative pain.

Ketorolac is a novel NSAIDs with potent analgesic effect. It is used orally in a dose of 10-20 mg 6 hourly for short term management of moderate to severe pain. Continuous use for more than 5 days is not recommended.¹

Acetaminophen's central analgesic actions are comparable to those of aspirin, but has a weak peripheral anti-inflammatory component. It does not elicit gastrointestinal irritation or prolong bleeding. Acute toxicity is minimal unless an overdose occurs, which may lead to hepatotoxicity. Analgesia by acetaminophen in the average adult becomes readily measurable at a dose of 300 mg and plateaus at 1,000 mg.¹¹ The introduction of selective COX-2 inhibitors has allowed specific targeting of PG production while minimizing adverse side effects.¹² Clinically available COX-2 inhibitors include rofecoxib, celecoxib and valdecoxib. As yet, valdecoxib has not been approved for the treatment of acute pain.¹³ Duration of action of rofecoxib is sufficiently long to permit single daily dosing. In a dose of 50 mg, rofecoxib is comparable to 400 mg of ibuprofen in onset and peak pain relief.^{14,15}

Opioids and Related Agents

In contrast to NSAIDs, opioids do not have an obvious ceiling effect for analgesia, that is, greater pain relief can be obtained by increasing the dose beyond a certain limit. Unfortunately, opioids cause undesirable side effects which limit their dosing.¹⁶

Morphine is the principal alkaloid in opium and considered as the prototype drug. It is a strong analgesic and higher doses can mitigate even severe pain. Suppression of pain is selective, without affecting other sensations or producing proportionate CNS depression. Morphine is rarely prescribed orally because most of the drug is metabolized in the liver before reaching the systemic circulation. The three most commonly used opioids for oral administration are codeine, hydrocodone and oxycodone. These agents have a high oral: parenteral efficacy ratio because a fraction of each drug is converted by the hepatic enzyme cytochrome P450 2D6 to a much more active metabolite (codeine - morphine, hydrocodone - hydromorphone, oxycodone - oxymorphone) and released into the bloodstream. The standard doses of opioids to produce pain relief in dentistry are codeine- 30-60 mg, hydrocodone- 5-10 mg and oxycodone 5-10 mg.¹²

Tramadol is a recently introduced centrally acting analgesic which relieves pain by two complementary mechanisms. It is a weak μ -receptor agonist, imbuing the drug with opioid-like activity. In addition, tramadol inhibits the reuptake of norepinephrine and 5-hydroxytryptamine, an antidepressant-like action and thus activates monoaminergic spinal inhibition of pain. Because of its weak opioid activity, tramadol exhibits less adverse effects. Relief of acute oral surgery pain with 50 mg of tramadol is similar to that of 60 mg of codeine.¹⁷

Combination Analgesics

A strategy commonly used to enhance the analgesic benefit is to combine two (or more) drugs with different mechanisms of action. Combining an NSAIDs with another NSAIDs or an opioid with another opioid, provides no

such benefit. In the case of NSAIDs, the maximum pain relief is already achieved by using a fully effective dose of a single agent. The combination can only produce increased adverse effects. With opioids, the increased analgesia, which could also have been obtained by using a larger dose of a single drug, is accompanied by heightened adverse effects that make such combinations intolerable.

The combination of acetaminophen or an NSAIDs with an opioid allows for increased analgesia because the drugs act through dissimilar mechanisms. Because they also have dissimilar side effects, summation of the intensity of these effects does not occur.¹⁸ It is unclear if adding acetaminophen to any NSAIDs already being taken at a ceiling analgesic dose provides any benefit.^{19,20} Resolution of this question depends on whether these drugs act on the same or different prostaglandin pathways involved in nociception.

Caffeine is an analgesic adjuvant that exerts no analgesic action by itself in humans but can enhance the potency of many NSAIDs. But improvement of the analgesic effect of "ceiling" doses of NSAIDs or acetaminophen by caffeine is uncertain.²¹

Precautions and Drug Interactions

All NSAIDs including the COX-2-specific agents should be avoided in patients who have exhibited an allergy like reaction such as urticaria, angioneurotic edema, bronchial asthma and acute hypotension to any NSAIDs.¹¹ Patients with bleeding disorders, platelet deficiency and gastrointestinal inflammatory or ulcerative disease should not receive NSAIDs with COX-1 activity. These are not recommended during pregnancy in the second and third trimester (possible premature closure of the ductus arteriosus, excessive bleeding or depressed uterine contractions during labor and delivery) and congestive heart failure or significant renal impairment (possible fluid retention). The use of aspirin in children may trigger Reye's syndrome in the presence of a viral infection.²²

Opioid analgesics are problematic in patients with impaired respiration, poorly controlled myasthenia gravis and severe inflammatory bowel disease. Morphine is contraindicated in patients with head injuries. For patients with a history of opioid drug abuse, consultation with the physician is advised to balance the need for effective analgesic medication against the concern of triggering addiction relapse.²³

Geriatric patients often exhibit diminished clearance of analgesics, increased plasma concentrations of free drug and increased pharmacologic effects. There is also a heightened risk for drug interactions since many elderly patients are already taking multiple medications. Precautions must be taken and proper dose adjustment should be done when prescribing analgesics for pediatric patients as age and body size can significantly influence their doses.

Analgesic Selection

Pain of mild to moderate intensity, as may follow extensive restorative dentistry or simple periodontal surgery, is best managed with acetaminophen or low doses ibuprofen. For controlling moderate to severe pain, as caused by acute pulpitis, ceiling doses of ibuprofen, diclofenac and rofecoxib are suitable. Acute post-operative painful conditions like surgical removal of impacted third molars are best managed by ceiling doses of ketorolac and diclofenac.

Acetaminophen-opioid combinations are the drugs of choice for moderate to severe pain when NSAIDs are contraindicated. Acetaminophen is taken in a dose of at least 600 mg and the opioid is used in a dose (codeine 60 mg, hydrocodone 7.5 to 10 mg, oxycodone 7.5 to 10 mg) that significantly increases relief without usually producing intolerable side effects. Several combinations of acetaminophen with either pentazocine, propoxyphene or tramadol can be used for patients who are truly allergic to morphine-like opioids. Table 1 lists the oral analgesics for a typical healthy adults and children.^{24,25}

Table 1: Oral Analgesics Dosage for Healthy Adults and Children

Drug	Recommended Dose (Adult)
Mild to moderate pain	
Acetamenophen 325 mg	2 tab.* q. 4 h #
Aspirin 325 mg	2 tab. * q. 4 h #
Ibuprofen 200 mg	1 tab. * q. 4 h #
Naproxen Sodium 220 mg	1 tab. * q. 6-8 h "
Moderate to severe pain	
Diclofenac potassium 50 mg	1 tab. * t.i.d †
Ibuprofen 200 mg	2 tab. * q. 4 h # or 3 tab. q. 6 h "
Ibuprofen 400 mg	1 tab. * q. 4 h #
Ibuprofen 600 mg	1 tab. * q. 6 h "
Ketorolac 20 mg	1 tab. * q. 6 h ", not to exceed 5 days
Rofecoxib 50 mg	1 tab. * q.d. ¶
Moderate to severe pain, when NSAIDs contraindicated or Opioids desired	
Acetamenophen 325 mg + Codeine 30 mg	2 cap.^ q. 4 h #
Acetamenophen 650 mg+ Hydrocodone 10 mg	1 tab. * q. 4-6 h #
Acetamenophen 650 mg+ Oxycodone 10 mg	1 tab. * q. 4-6 h #
Acetamenophen 325 mg+ Tramadol 37.5 mg	2 tab. * q. 4-6 h #, maximum 8 tab / 24 hrs.
Drug	Recommended Dose (Children)
Acetaminophen 10-15 mg/kg body weight	1 tab. * q. 4-6 h # (Also available in an elixir form)
Ibuprofen Age 2-12 - 10 mg/kg body weight	1 tab. * q. 6-8 h " (Also available in an elixir form)
Over age of 12 - 200-400 mg	1 tab. * q. 4 h # (Also available in an elixir form)

* - Tablet

- quaque quarta hora (every 4 hours)

" - quaque sex- octa hora (every 6 - 8 hours)

† - ter in die (a thrice-daily dosage)

¶ - quaque die (every day)

^ - Capsule

NSAIDs before adding an opioid, optimize dose and frequency of each drug, following a fixed dosing schedule instead of 'prn' basis and avoid chronic use of any analgesic whenever possible. Our goal should be to use these drugs optimally to treat dental pain most effectively

Conclusion

From a dentists' perspective, we are able to choose from a plethora of medications to provide patients with pain relief, but trying to judge the relative efficacy of analgesics is not easy. One must remember that the best means of managing pain is to remove the source of pain as quickly as possible. Each drug regimens should be individualized based on pain severity and medical history. Certain guidelines should be followed while prescribing analgesics like maximize the

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