Quality Resource Guide

Alternatives to Opioid Analgesics in Dental Practice

Author Acknowledgements

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Educational Objectives

Following this unit of instruction, the practitioner should be able to:

1. Understand the principles of prescribing analgesics in dental practice;
2. Describe the actions, rationale for selection and common adult dosage regimens for the analgesics discussed in this Guide;
3. Describe the major contraindications and warnings associated with analgesics prescribed in dental practice and discussed in this Guide;
4. Describe the major adverse drug reactions and drug interactions associated with analgesics prescribed in dental practice and discussed in this Guide;
5. Understand the scientific basis for the current recommendations for the use of non-opioid analgesics in dental practice.

MetLife designates this activity for **1.0 continuing education credits** for the review of this Quality Resource Guide and successful completion of the post test.

The following commentary highlights fundamental and commonly accepted practices on the subject matter. The information is intended as a general overview and is for educational purposes only. This information does not constitute legal advice, which can only be provided by an attorney.

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Introduction and Principles of Pain Management in Dentistry

Analgesics play an important role in the management of dental pain, primarily as adjuncts to definitive interventions. Traditionally, non-opioid/opioid combinations (acetaminophen with codeine or hydrocodone) have been the analgesics of choice for the routine management of pain in dentistry. Recently, however, a strong association between opioid prescribing and the current "opioid crisis" has been convincingly demonstrated, and it appears that reductions in legitimate opioid prescribing were linked to increases in heroin use and are now linked to increases in the use of fentanyl and illicitly manufactured fentanyl congeners.[1] The previous rationale for using opioids to control dental pain was not entirely evidence-based and included the perception that "controlled substances" should be more efficacious than non-addictive agents.[2] However, concerns over increasing abuse and diversion of opioids, as well as increasingly strong scientific evidence for superior pain relief provided by non-steroidal anti-inflammatory drugs (NSAIDs), have combined to fundamentally change the contemporary approach to the management of acute dental pain.[3] Following the approval of ibuprofen by the Food and Drug Administration in 1974, an ever-expanding array of drugs in the NSAID class, primarily for the management of osteoarthritis and musculoskeletal pain, requires careful evaluation of which agents are best-suited for use in dentistry.

This Quality Resource Guide (QRG) will focus on non-opioid oral analgesics for control of acute pain, with an emphasis on high-level scientific evidence. The management of chronic orofacial pain is beyond the scope of this QRG and will not be covered.

There are several important principles that must be considered prior to prescribing an analgesic for a dental patient:

1. Analgesics are adjuncts to caries removal and surgical interventions (tooth extraction, pulpectomy, incision-and-drainage) and should not be used in place of these procedures in the management of acute dental pain;
2. The selection of an analgesic must be based upon the patient's medical history and current disorders, and take into account the possibility of adverse events and adverse drug/drug interactions;
3. An analgesic regimen should be based upon the expected level and duration of pain, taking into consideration systemic conditions such as cardiovascular, gastrointestinal and allergic conditions and defined clinical endpoints (reduction of pain, swelling);
4. While no longer recommended as drugs of first choice for dental pain, the opioids, particularly those marketed in combination with acetaminophen, remain important alternatives when NSAIDs are inappropriate due to allergy and other medical conditions (described below).

Pharmacologic Characteristics of NSAID Analgesics for Acute Postoperative Dental Pain

There are several chemical classes of NSAIDs, many of which are used in various medical conditions, especially osteoarthritis. The most important class for the control of pain in dentistry is the propionic acid group, which includes ibuprofen (Advil®), naproxen (Aleve®), and ketoprofen (Orudis®). All of these agents possess analgesic, anti-inflammatory, antipyretic and antiplatelet therapeutic actions, and are ideally suited for applications in inflammatory dental conditions (acute apical periodontitis, symptomatic irreversible pulpitis). They act by inhibition of cyclooxygenase enzymes (COX-1 and COX-2), which reduces the synthesis of prostaglandins (PGs), and their analgesic action is attributable primarily to a reduction of PGE2 and F2α, which are synthesized rapidly after tissue damage and sensitize nociceptive nerve endings to a wide variety of noxious stimuli. Importantly, inhibition of PG synthesis occurs relatively early in painful inflammatory conditions, so NSAID therapy should commence as early as feasible in pain management. While aspirin is typically classified in this group, it can no longer be recommended for postoperative pain control due to its higher incidence of adverse effects and lower comparative efficacy.

Acetaminophen

High-level scientific evidence from systematic reviews of acute postoperative pain in adults suggests that, based on number-needed-to-treat (NNT), acetaminophen administered alone is not a particularly good analgesic.[3] This has been confirmed in randomized controlled trials of post-endodontic pain as well.[5] However, when used in combinations, acetaminophen appears to act synergistically with both NSAIDs and opioid analgesics and the combination of 200-400 mg ibuprofen plus 500-1,000 mg acetaminophen (taken together) results in the best NNT values in the oral surgical pain model.[4] Taken simultaneously, this combination does not result in adverse effects greater than those observed in placebo groups when used on a short-term basis.[3] However, it should also be noted that the maximum daily adult dose of acetaminophen from all sources (Rx and OTC) should not exceed 4,000 mg.[3,4] Hepatotoxicity may occur from excessive acetaminophen intake or from interactions with chronic alcohol use. While unusual, allergy to acetaminophen can occur and would absolutely contraindicate use of this agent. Studies reported in endodontics have emphasized the use of 600-mg, rather than 400-mg, doses of ibuprofen,[7] and it should be noted that repeating this dose on a 6- to 8-hour basis does not exceed the maximum daily adult dose of 3,200 mg currently recommended the manufacturers.

In those patients in whom neither acetaminophen nor opioids can be used but NSAIDs are not contraindicated, two NSAIDs are available which

have demonstrated NNT values less than 2 in the dental model without acetaminophen—ketoprofen (Orudis™) and diclofenac (Cataflam™).[3]

A summary of the comparative pharmacologic characteristics of propionic acid NSAIDs, acetaminophen and opioid analgesics is presented in **Table 1**.

Prescribing Considerations

1. For the management of acute post-surgical dental pain (including pain of endodontic origin), in the absence of any significant contraindications, therapy should begin with a standard dose of a combination orally administered first choice agents (ibuprofen with acetaminophen).[5-8]
2. For optimal pain relief, the combination of 200-400 mg ibuprofen with 500-1,000 mg acetaminophen has been shown to provide pain relief that is superior to virtually all acetaminophen/opioid combinations and COX-2 selective NSAIDs.[2] Patients may be unaccustomed to taking these two drugs together, so the practitioner must reinforce the concept of simultaneous administration to ensure good pain relief. The use of combinations of drugs for pain, rather than individual agents, is advantageous and capitalizes on the phenomenon of pharmacologic synergism.
3. Because peak pain associated with dental extractions appears to occur within the first 6-8 hours postoperatively and then decline over the next 2 to 3 days, short-term administration of the ibuprofen/acetaminophen combination can be employed.
4. A need for a sedative effect (such as post-operative anxiety), especially in the first 24 hours postoperatively, may warrant the addition of an opioid analgesic in combination with the NSAID, when the patient's activities would not be affected by possible CNS depression.
5. Warnings with analgesic therapy should be issued verbally and in writing on the prescription. They should include the possible development of allergic reactions, as well as GI disturbances, increased bleeding risk, adverse interactions between acetaminophen and alcohol, or acetaminophen overdose.

Adverse Effects

NSAID analgesics, as prescribed in dentistry, are generally well tolerated. With the exception of allergy, most adverse effects from short-term use of NSAIDs are related to their effects on the gastrointestinal tract and platelets. NSAIDs inhibit the formation of gastroprotective PGs, and this irritant effect, combined with their antiplatelet effect, can result in ulcerations and GI bleeding. Short-term use of NSAIDs has been shown to be relatively safe when administered for dental pain.[7]

Table 1 - Comparative Pharmacologic Characteristics of Non-steroidal Anti-inflammatory Drugs (NSAIDs)*, Opioids and Acetaminophen Analgesics Available in the U.S.[4]

Characteristic	NSAIDs	Opioids	Acetaminophen	Comment
Available OTC	Yes	No	Yes	Emerging evidence favors gel and liquid preparations.
Tolerance, dependence	No	Yes	No	Opioid tolerance and dependence are unlikely to occur with short-term use (<5 days).
CNS depression	No	Yes	No	A sedative effect of opioids may be desirable in some circumstances.
Anti-inflammatory	Yes	No	No	Principal advantage of NSAIDs.
Anti-pyretic	Yes	No	Yes	Beneficial in the presence of infection.
Analgesic	Yes	Yes	Yes	NSAIDs act primarily peripherally at the site of tissue injury, while opioids act centrally (CNS). Combinations are generally superior to single-agent regimens.
Antiplatelet agents (including aspirin)	Yes	No	No	Increased bleeding risk is associated with NSAIDs, primarily if taken preoperatively; the effect is reversible (unlike aspirin, which is irreversible).
GI dysfunction	Yes	Yes	No	In addition to nausea and vomiting, opioids are associated with constipation. NSAID-related GI irritation is typically seen during prolonged administration (>5 days).

** propionic acid class*

Ingestion of high doses of NSAID analgesics is associated with nephropathy, and the risk of this complication increases in elderly patients, as well as patients who are dehydrated[9] or have pre-existing renal insufficiency, heart failure or diabetes. It should be noted that dehydration could be present in individuals with symptomatic irreversible pulpitis who have experienced diarrhea and/or nausea and vomiting (possibly induced by self-prescribed antibiotics and/or analgesics) and who are not well nourished/hydrated due to dental pain. This is particularly problematic when patients have ingested over-the-counter NSAIDs or acetaminophen before receiving dental treatment.

Since renal blood flow and urine formation are in part regulated by physiologic PGs, blood pressure may be elevated by the ingestion of NSAIDs, and this should be considered when designing an analgesic regimen for patients with hypertension and other cardiovascular disorders.

Bleeding is associated with all NSAIDs, and increased intraoperative and postoperative bleeding must be anticipated and dealt with effectively, including the use of careful surgical technique, suturing and other hemostatic measures (oxidized cellulose packs).

The risk of allergic and adverse respiratory reactions to NSAIDs should be evaluated through a careful medical history, especially in patients with a prior history of aspirin allergy, asthma and reactive airway disease.

Pregnancy constitutes a contraindication to the use of NSAIDs, particularly in the first and third trimesters.

Drug Interactions

NSAID analgesics are capable of adversely interacting with other dental and medical drugs, both through pharmacodynamic and pharmacokinetic mechanisms. The most significant adverse interactions for commonly prescribed NSAID analgesics are listed in **Table 2**.

Corticosteroids

In some cases, anti-inflammatory corticosteroids may be beneficial in providing short-term pain relief, particularly in cases of inflammation associated with apical periodontitis, acute apical abscess and third-molar extraction. Based on recent scientific evidence, both methylprednisolone and dexamethasone can be utilized in such situations, although an injection is required.[11,12] Alternatively, orally-administered corticosteroids can be used to suppress inflammation, both pre- and postoperatively. At this time, however, it appears that the best pain-control outcomes to be derived from perioperative corticosteroids are obtained from preoperative, intramuscular, rather than oral, postoperative administration.[13] Based on its pharmacologic profile and availability, dexamethasone can be considered as a front-line agent.

Table 2 - Clinically Significant Drug Interactions Involving NSAID Analgesics Used in Dentistry (modified from reference 10)

Primary Drug	Action	Interaction (and Effect)
Alcohol	Enhanced by NSAIDs	Increased GI irritation, nausea, GI pain and bleeding.
Diuretics, antihypertensive drugs	Antagonized by NSAIDs	Increased salt and water retention with increased blood pressure.
Coumarins (including warfarin)	Enhanced by NSAIDs	Increased risk of bleeding.
Antiplatelet agents (aspirin, clopidogrel)	Enhanced by NSAIDs	Increased risk of bleeding; increased risk of thromboembolism (ibuprofen blocks the antiplatelet effect of aspirin when the drugs are taken concurrently).
Direct oral anticoagulants (rivaroxaban, dabigatran)	Enhanced by NSAIDs	Increased risk of bleeding.
Potassium-sparing diuretics	Enhanced by NSAIDs	NSAIDs may increase serum potassium levels.
Potassium supplements	Enhanced by NSAIDs	NSAIDs may increase serum potassium levels.
Cancer chemotherapeutic agents	Enhanced by NSAIDs	Increased risk of GI ulceration.
Selective Serotonin Reuptake Inhibitors (SSRIs)	Enhanced by NSAIDs	Increased risk of GI ulceration and bleeding.
Corticosteroids	Enhanced by NSAIDs	Increase salt and water retention; increased risk of GI ulceration.

Less significant drug interactions are also possible - the clinician is urged to consult the complete prescribing information for all drugs prescribed.

For elderly and medically compromised patients with systemic disease that could impact drug metabolism and/or excretion, consultation with the patient's physician is recommended.

Pre-Emptive Analgesia

NSAIDs have been evaluated for use pre-emptively (pre-operative administration to reduce post-operative pain). The reader is referred to an excellent update on this topic.[14] Typically, single-dose ibuprofen, administered approximately one-hour before a procedure, is recommended, based on limited evidence. When used in this manner, intraoperative bleeding risk is increased, and the importance of hemostasis during the dental procedure cannot be overstated when employing this pain-control strategy.

Liposomal Bupivacaine

The use of the long-acting local anesthetic bupivacaine hydrochloride for dental local anesthesia has been advocated as a means of reducing pain and the need for analgesic medications following dental surgery. When used by buccal infiltration in endodontically-involved teeth, a randomized, double-blind trial of liposomal bupivacaine versus infiltration of aqueous bupivacaine hydrochloride (as used in dental cartridges) failed to demonstrate significantly better postoperative pain control by the liposomal preparation.[15] In third molar impaction surgery, liposomal bupivacaine provided better postoperative pain than placebo with no greater incidence of adverse events, although the study could not be considered conclusive due to extensive protocol violations in the phase 3 placebo-controlled study.[16] Finally, a more recent systematic review with 63 included studies concluded that the majority of randomized controlled trials of the efficacy of liposomal bupivacaine for postoperative pain relief relative to placebo or active drugs do not support claims of superiority of liposomal bupivacaine.[17] At this time, dental practitioners should carefully consider this evidence, as well as the costs of liposomal bupivacaine, when determining how this agent will integrate into their overall protocol for managing acute postoperative pain.

Summary

Dentists should continue to consider emerging evidence for the use of non-opioid analgesics, especially in view of the ever-increasing problem of opioid abuse and diversion. Dentists can confidently prescribe a NSAID or recommend OTC combinations for excellent relief of acute dental pain, based on high-level scientific evidence. In those cases in which OTC combinations may be contraindicated, other pharmacologic strategies should be employed in the early postoperative period, including placement of liposomal bupivacaine where wound anatomy permits and/or the administration of pre-, intra- and postoperative corticosteroids.

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1. **Oral analgesics of choice in aspirin-allergic dental patients include:**
   a. opioid analgesics.
   b. acetaminophen.
   c. naproxen.
   d. Both a and b

2. **NSAIDs produce all of the following EXCEPT:**
   a. Reduction of body temperature when a fever is present
   b. CNS depression
   c. Reduction of inflammation
   d. Analgesia

3. **Which of the following can produce serious systemic toxicity when taken with an NSAID?**
   a. Aspirin
   b. Omeprazole
   c. Amoxicillin
   d. Oxycodone

4. **NSAIDs produce analgesia primarily by:**
   a. activation of descending spinal inhibitory pathways.
   b. inhibition of cyclooxygenase enzymes.
   c. blockade of Histamine-1 receptors in peripheral nerves.
   d. depression of cortical sensory neurons.

5. **All of the following are true regarding analgesics used in dentistry EXCEPT:**
   a. Opioids are the drugs of first choice.
   b. Acetaminophen should be used in combination with another analgesic.
   c. Useful NSAIDs are typically from the propionic acid class.
   d. Corticosteroids should be avoided in patients taking NSAIDs.

6. **NSAIDs may antagonize the therapeutic effect of drugs used to treat:**
   a. hypertension
   b. seizure disorders
   c. bacterial infections
   d. cancer

7. **All of the following are contraindications to the use of NSAIDs EXCEPT:**
   a. aspirin allergy
   b. pregnancy
   c. bleeding disorders
   d. osteoarthritis

8. **Alcoholic beverages should be avoided when taking an NSAID. Acetaminophen synergistically enhances the analgesic effects of NSAIDs.**
   a. Both statements are true
   b. The first statement is true, the second is false
   c. The first statement is false, the second is true
   d. Both statements are false

9. **When taken for pain in adults, the correct dose of acetaminophen taken in combination with ibuprofen is:**
   a. 200 - 400 mg
   b. 81 mg
   c. 500 - 1,000 mg
   d. 325 mg

10. **The greatest analgesic efficacy of corticosteroids is achieved when they are administered:**
    a. preoperatively/parenterally.
    b. intraoperatively/parenterally.
    c. preoperatively/orally.
    d. postoperatively/orally.

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