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The efficacy of combination analgesic therapy in relieving dental pain

DONALD R. MEHLISCH, M.D., D.D.S.

Patients typically associate dental care with pain. Pain has both physiological and psychological components, and an experience of poorly managed pain related to dental treatment can lead patients to avoid or postpone treatment,¹ as well as make them more difficult to treat and less likely to comply with prescribed regimens.²

Medications that reduce pain improve clinical outcomes.^{3,4} The development of new pain management strategies affords dental clinicians with additional treatment options for acute pain management (Figure). Preoperative administration of some analgesics, for example, has been shown to reduce the onset of postoperative pain.^{5,6} Another approach involves combining analgesics that target both peripheral and central pain pathways to deliver comparable analgesia at lower—and hence more tolerable—doses of the component drugs. Combining drugs with different time to onset⁷ or duration of action^{8,9} also can improve the range of

analgesic effect. Combining analgesics with differing sites of action, modes of action, onset and duration, in other words, can greatly enhance their capacity to minimize pain, be tolerated better and reduce recovery time.

CHARACTERISTICS OF PAIN

Pain can be either acute or chronic. Acute pain typically is associated with recent tissue injury and has a short duration.¹⁰ Chronic pain, however, often has an unclear etiology and can last for years, persisting long after an injury has healed. Dental pain typically is acute in

Background. An experience of poorly managed pain related to dental treatment can lead patients to avoid or postpone treatment. The development of new pain management strategies equips dental clinicians with additional treatment options that can provide more effective pain relief.

Literature Reviewed. The author reviewed dental and medical literature dealing with the safety, efficacy and mechanisms of action of common analgesic treatments.

Conclusions. For the treatment of mild to moderate pain, acetaminophen and nonsteroidal anti-inflammatory drugs, or NSAIDs, continue to be the most appropriate options. The use of cyclo-oxygenase-2-inhibitor NSAIDs should be strongly considered for use with patients at risk of experiencing gastrointestinal toxicity. The pathophysiology of pain is a complex central and peripheral nervous system process, and the use of combination analgesics that act at multiple pain sites can improve pain relief after a dental procedure. For moderate to moderately severe pain, tramadol or combination medications such as tramadol with acetaminophen or codeine with acetaminophen are appropriate. For severe pain, use of opioids or opioid combinations is advised.

Clinical Implications. Providing appropriate treatment after dental surgery requires a careful medical history and an educated anticipation of the level of pain the patient may encounter. New analgesic options are available and should be considered, particularly combination analgesics, which can provide faster onset and prolonged duration of action and can combat pain at multiple sites of action.

nature and can be associated with relatively noninvasive procedures such as tooth extraction, endodontic therapy or scaling of the periodontal area, as well as more traumatic procedures that can produce prolonged postoperative pain



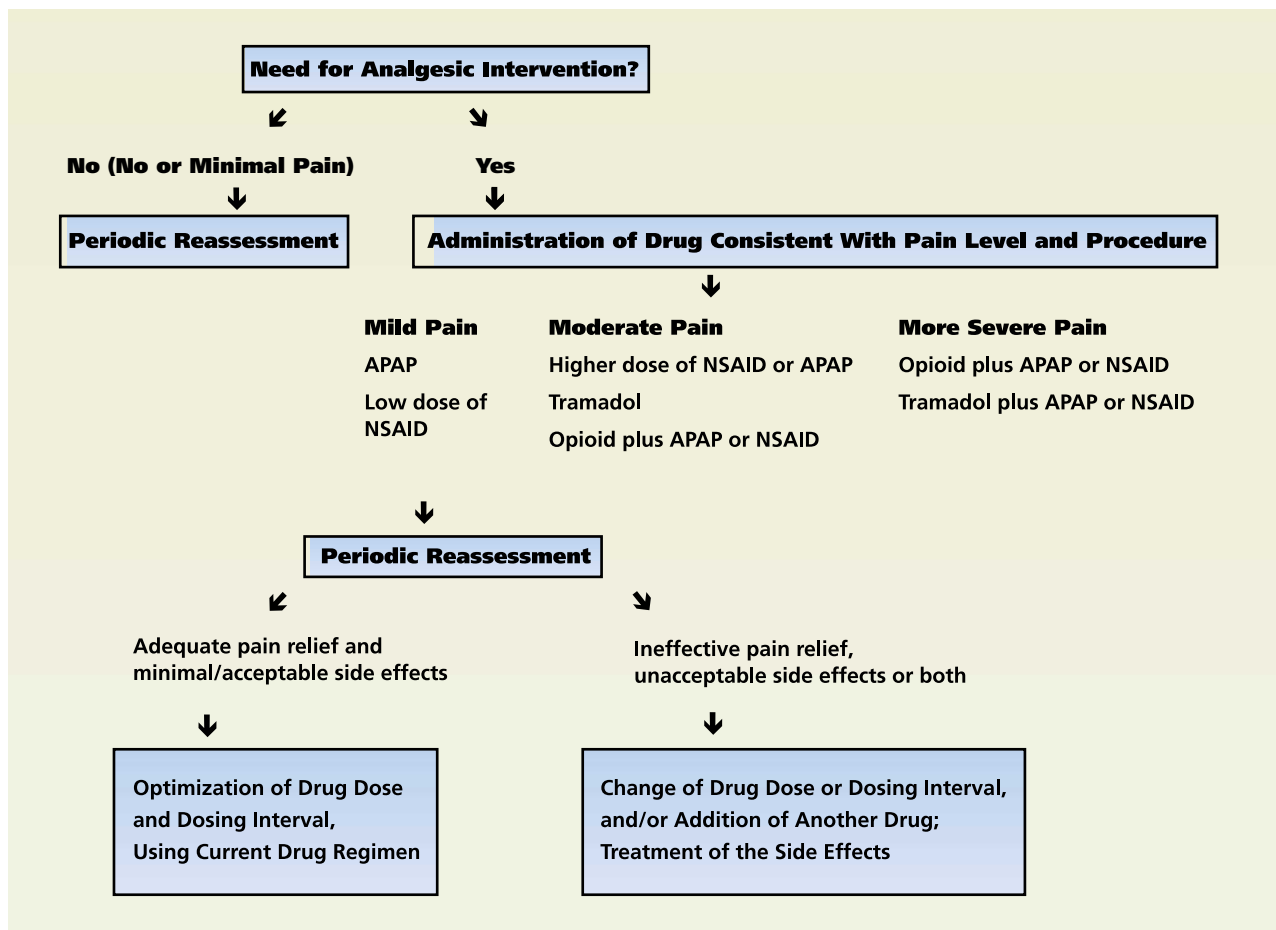


Figure. Management of postoperative dental pain. Based on information from Dionne and Gordon⁴⁴ and Hargreaves and colleagues.⁶⁹ APAP: Acetic acid and *p*-aminophenol, commonly known as acetaminophen. NSAID: Nonsteroidal anti-inflammatory drug.

(such as surgical removal of bony impactions and osseous periodontal surgery). Longer-term analgesic therapy also may be indicated for patients with chronic orofacial pain.

Preliminary observations of various types of operative pain indicate that the biological and psychological foundation for long-term persistent pain is in place within hours of injury.¹¹ Even a brief painful stimulus can produce lasting changes in cells within the spinal cord.¹² Tissue injury causes a cascade of events (including peripheral inflammation) that release various mediators into the local environment.¹³ These mediators activate the primary afferent nerves or sensitize local nerve receptors, which, in turn, can evoke changes at the level of the spinal cord, a process referred to as “peripheral sensitization.”¹⁴ This process is responsible for the development of hyperalgesia beyond the damaged site. If acute pain is not properly treated, prolonged activation

of the pain pathways can lead to further neurophysiologic changes collectively called “central sensitization,” which may prolong recovery and convert acute pain to a chronic condition.¹⁵ Proper analgesic treatment can reduce this risk.¹¹

ASSESSING ANALGESIC EFFICACY FOR DENTAL PAIN

There is an increasing need for clinical models that accurately reflect the efficacy of varied analgesics. Extraction of an impacted third molar is a model commonly used to test the efficacy of analgesics for acute dental pain,¹⁶ providing U.S. Food and Drug Administration–accepted evaluations of analgesic therapies.¹⁷ Third-molar extraction induces pain that generally is consistent in severity, allowing for good discrimination between weak and strong analgesics.¹³ However, the procedure has limitations. Demographically, it tends to enlist a young, healthy, homogeneous

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population seeking elective surgery, which is clinically useful but may not be representative of all dental patients in pain. It also tests pain of a fairly limited range and duration (moderate to severe postoperative pain, which usually occurs within the first three hours postoperatively, peaks after approximately six hours, and can last for three to five days¹⁸) and generally favors analgesics of a particular mechanism of action (anti-inflammatory). Other factors, such as baseline pain, can also effect results; for example, Averbuch and Katzper¹⁷ examined two third-molar extraction studies in which baseline pain was rated as moderate in one study and severe in the other. They determined that higher baseline pain is associated with a greater ability to determine pain relief.

Acute tissue trauma causes inflammation that increases the responsiveness of local nociceptors. The activity generated by these neurons is relayed to the dorsal horn neurons in the spinal cord, leading to pain perception by the brain.¹³ Because of the tissue trauma involved, the third molar extraction model is influenced significantly by anti-inflammatory drug therapy. Although third molar extraction has provided a useful clinical model, more robust models that accurately test different kinds of pain and analgesics with differing mechanisms of action are also needed.

CLINICAL PROFILES OF COMMON ANALGESICS

Characteristics of analgesics commonly used for that management of dental pain are summarized in the table.

Acetaminophen. Acetic acid and *p*-aminophenol, or APAP—commonly known as acetaminophen—is classified as a nonopioid analgesic generally used for mild to moderate pain. Its actions are both analgesic and antipyretic, and it has rapid onset of analgesic action.^{7,19} Although its mechanism of action is unclear, possible mechanisms include the inhibition of nitric oxide pathways²⁰ and the reversal of hyperalgesia induced by either N-methyl-D-aspartate, or NMDA, or substance P.^{21,22} Acetaminophen is thought to be a poor inhibitor of prostaglandin synthesis, so unlike nonsteroidal anti-inflammatory drugs, or NSAIDs, it has little anti-inflammatory action. It generally is safe for acute pain, although very high single doses also have been associated with cases of hepatotoxicity²³ and alcohol intoxication has been shown to predispose patients to hepato-

toxicity at normal doses.²⁴

Acetaminophen 500 milligrams was superior to placebo for treatment of dental pain associated with third-molar extraction, although pain relief was brief, peaking one hour after administration.²⁵ A large meta-analysis examining the efficacy of acetaminophen 600 or 650 mg as monotherapy showed it to be superior to placebo.²⁶ Significantly more pain relief was provided by acetaminophen 1,000 mg compared with placebo, as determined by pain intensity and pain relief scores for up to five hours after oral surgery,²⁷ although pain relief was maximal at one to two hours after administration.²⁸ A large meta-analysis examining the efficacy of acetaminophen found pain relief with acetaminophen 1,000 mg was maximal for up to four hours after administration.²⁹

Acetaminophen 1,000 mg has been shown to be an effective treatment compared with placebo for extraction of impacted third molars and for various other oral surgeries, including difficult extractions, alveolectomy, multiple extractions, apicoectomy, biopsy and deep gingival curettage.⁷ Although these studies show that acetaminophen provides rapid pain relief superior to that of placebo, it has been suggested that because of its ceiling-dose effect, acetaminophen is a limited analgesic.²⁹ Acetaminophen appears to be a good analgesic for mild pain, but its relatively short-acting analgesia limits its usefulness as a monotherapy for the treatment of moderate to severe postoperative pain.

NSAIDs. NSAIDs have been the traditional treatment for moderate pain and inflammation. NSAIDs such as ibuprofen, ketorolac, flurbiprofen, ketoprofen, diclofenac, aspirin and aspirin derivatives diminish postoperative hyperalgesia peripherally.^{30,31} NSAIDs act primarily through inhibition of cyclooxygenase, or COX, enzymes 1 and 2. COX-1 is distributed throughout the body and has a role in protection of stomach mucosa, platelet action and kidney function.³² COX-2 is important in the production of prostaglandins,³³ is expressed in only a few specialized tissues and is induced during inflammation. Inhibiting COX-2 blocks prostaglandin formation and ultimately prevents inflammation and sensitization of the peripheral nociceptors. Inhibiting COX-1, however, attenuates its gastroprotective action, suggesting that the gastrointestinal, or GI, toxicity associated with long-term use of NSAIDs³⁴⁻³⁶ is related to their effects on

TABLE

COMPARISON OF MAJOR ANALGESICS USED FOR THE MANAGEMENT OF DENTAL PAIN.

CHARACTERISTIC	ANALGESIC				
	Acetaminophen	Nonselective NSAIDs*	COX-2† NSAIDs	Traditional Opioids	Tramadol
Mechanism of Action	Reversal of NMDA‡/ substance P-induced hyperalgesia? Inhibition of nitric oxide pathways?	Inhibition of COX-1 and COX-2 enzymes	Selective inhibition of COX-2 enzyme	Inhibition of nociceptive transmission through μ-opioid receptor binding	Low affinity binding to μ-opioid receptor and inhibition of norepinephrine and serotonin reuptake
Pain Level Treated	Mild to moderate	Moderate	Moderate	Moderate to severe	Moderate to moderately severe
Efficacy as Monotherapy for Dental Pain	+§	+	+	+/-¶	+
Ceiling Effect	Yes	Yes	Yes	Yes/no	No
Efficacy in Combination Therapy for Dental Pain	Increased efficacy with opioids, tramadol	Increased efficacy with opioids, tramadol	Not evaluated in published clinical trials	Increased efficacy with acetaminophen, NSAIDs	Increased efficacy with acetaminophen, NSAIDs
Side Effects	Minimal, except hepatotoxicity (generally at high doses) or at normal doses with pre-existing liver disease, including intoxication or alcoholism	Multiple gastrointestinal, or GI, effects; bleeding; cardiovascular, renal and hepatic side effects; drug interactions	Fewer GI effects; other side effects similar to those with nonselective NSAIDs; drug interactions	Respiratory depression, sedation, other central nervous system side effects; nausea; dizziness; constipation; dependence; drug interactions	Nausea; dizziness; drug interactions; fatigue; reduced or minimal opioid side effects; low risk of abuse/seizures; drug interactions
Use in Elderly	Yes	With caution	With caution	With caution	Yes

* NSAIDs: Nonsteroidal anti-inflammatory drugs.
 † COX-2: Cyclo-oxygenase enzyme 2.
 ‡ NMDA: N-methyl-D-aspartate.
 § +: Acceptable.
 ¶ +/-: Some traditional opioids are partial agonists, having both agonist and antagonist properties.

COX-1. Long-term use of NSAIDs also has been associated with renal toxicity^{32,37}; inhibition of both COX-1 and COX-2 may be involved.³⁸ Elderly patients or those with a history of gastric bleeding, renal compromise or cardiovascular problems should not be prescribed long-term or high-dose NSAIDs.^{39,40} Also, NSAIDs have been shown to interact with several antihypertensive agents,^{41,42} which may compromise blood pressure control. The most common short-term side effects of NSAID usage are dyspepsia, diarrhea and abdominal pain.⁴³⁻⁴⁶ NSAIDs generally require a higher dose to

achieve maximum anti-inflammatory action than to achieve analgesic action. For example, 200 to 600 mg of ibuprofen four times per day or 800 mg three times per day may be needed for an analgesic effect, but 2,400 to 3,200 mg per day may be needed for an anti-inflammatory effect.⁴³ However, it is important to understand that the highest FDA-recommended daily dose is 2,400 mg. Also, a meta-analysis determined that recommended and higher-than-recommended single doses of NSAIDs produced comparable changes in pain scores, indicating a ceiling dose effect for analgesia.⁴⁷

Another meta-analysis of randomized controlled clinical studies that included studies of dental pain found ibuprofen given in doses of 50 to 400 mg to be superior to placebo at all dose levels.⁴⁸ Ibuprofen 400 mg was statistically superior to placebo for four hours after third-molar-impaction surgery,^{7,49} as well as for other oral surgeries such as difficult extractions, alveolectomy, multiple extractions, apicoectomy, biopsy or deep gingival curettage.⁷ Peak analgesia was reached at four hours after study medication was administered.⁴⁹ Additionally, Mehlisch and colleagues⁷ determined that monotherapy with ibuprofen managed dental pain better than did acetaminophen.

Ketorolac is a potent NSAID that is administered intravenously or intramuscularly and significantly reduced pain after endodontic surgery.⁵⁰ Ketorolac 60 mg/2 milliliters provided significantly more pain relief than did placebo at 12 and 24 hours after intracanal medication administration, although there was no difference at six and 48 hours.⁵⁰ Ketoprofen 100 mg was reported to have analgesic efficacy similar to that of acetaminophen 1,000 mg for pain management after surgical removal of impacted third molars, and both treatments were more effective than placebo.⁵¹ However, acetaminophen produced a more rapid onset of pain relief than ketoprofen.⁵¹

Several studies have demonstrated that monotherapy with the NSAIDs diflunisal, flurbiprofen, ibuprofen and ketorolac is more effective for pain relief than either acetaminophen 600 mg with codeine 60 mg or acetaminophen 650 mg with codeine 60 mg.^{13,52-54}

COX-2 NSAIDs. COX-2 NSAIDs, which selectively inhibit the COX-2 isoenzyme, were developed to limit NSAID adverse effects.⁴⁶ The two currently available COX-2-selective inhibitors, celecoxib and rofecoxib, are characterized by the following:^{36,45,46,55-58}

- less risk of GI ulceration than nonselective NSAIDs;
- similar types of other GI side effects, such as abdominal pain, dyspepsia, diarrhea and nausea;
- lack of effect on platelet function, unlike nonselective NSAIDs;
- renal toxicity similar to that of other NSAIDs;
- generally long duration of action, with once-

daily administration for rofecoxib and once- or twice-daily administration for celecoxib.

However, while COX-2 therapy may reduce the risk of GI ulcerations, recent evidence indicates that COX-2 therapy may not reduce the risk of cardiovascular complications.^{36,55}

Several studies have examined the role of the COX-2 NSAIDs celecoxib and rofecoxib in managing dental pain.^{59,60} Rofecoxib has been shown to be as efficacious as ibuprofen in dental pain and also more efficacious than celecoxib.^{59,61,62} Because of COX-2 inhibitors' demonstrated safety advantages, and because of rofecoxib's similar efficacy to that of nonselective NSAIDs in dental patients, these drugs appear to offer important benefits and may be used more frequently in

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Some of the side effects seen with opioids are especially troublesome in patients receiving ambulatory outpatient care in the dental office.

dental pain management.^{45,56} COX-2 NSAIDs may be an appropriate choice for patients for whom acetaminophen provides inadequate pain relief, who cannot tolerate nonselective NSAIDs or for whom nonselective NSAIDs should not be used owing to risk of developing GI complications.⁵⁶ Additionally, COX-2 NSAIDs have costs similar to those of brand-name NSAIDs, but much higher costs compared with those of generic and over-the-counter nonselective

NSAIDs.^{46,56} However, they may actually save costs if they have similar efficacy but require less prevention, monitoring and treatment of GI adverse effects, have a lower risk of causing bleeding complications and so forth.⁵⁶

Opioids. Opioids act on the central nervous system primarily by binding to μ -opioid receptors and impeding transmission of nociception while supraspinally activating inhibitory pathways that descend to the spinal segment. Opioids are thought to obstruct the release of substance P through the μ -opioid receptors.^{63,64} Side effects—including nausea, constipation, dizziness, sedation and respiratory depression—are common with opioid therapy.^{65,66} Some of the side effects seen with opioids, such as physical and mental impairment, are especially troublesome in patients receiving ambulatory outpatient care in the dental office. However, the relative risk of opioidlike side effects varies with different opioids.⁶⁷

Although opioids as a class are effective analgesics, some commonly used formulations show poor analgesic efficacy for dental pain, and sim-

ilar results can be achieved with other drugs with less severe side effects.⁶⁸ Codeine alone has not been found as effective as other common analgesics for relief of postextraction pain. Oxycodone, hydrocodone and propoxyphene are about as effective as codeine, and dihydrocodeine, pentazocine and meperidine exhibit no advantages over codeine orally and can even be less effective.⁶⁹

Codeine 30 to 90 mg has somewhat better pain relief and pain intensity scores than placebo,^{16,53} and oxycodone 5 mg provided better pain relief than placebo after third-molar extraction.²⁵ However, a recent literature review of dihydrocodeine for postoperative pain determined that dihydrocodeine did not provide pain relief with 30 mg as determined by total pain relief, or TOTPAR, or the sum of pain intensity differences, or SPID, over four to six hours.²⁶ Similarly, single doses of propoxyphene 65 mg were not significantly superior to placebo in effectiveness, as determined by a quantitative systematic review of various surgeries.²⁶ As a monotherapy, codeine 60 mg produced pain relief identical to that provided by acetaminophen 600 mg for postoperative pain.⁷⁰ Bentley and Head²⁸ found that patients treated with acetaminophen 1,000 mg required less remedication than those treated with codeine 60 mg after third-molar surgery. Additionally, single doses of hydrocodone 30 mg or 60 mg were not superior to a single dose of ibuprofen 400 mg in a postoperative pain model of moderate to severe intensity.²⁶

The high risk of major side effects—an important concern in ambulatory patients treated in the outpatient department or dental office—combined with the relative lack of oral efficacy may relegate opioids to limited use for relief of dental pain.⁶⁹ Their role in combination therapy far outweighs their usefulness as monotherapy.

Tramadol. Tramadol is a synthetic, centrally acting analgesic indicated for moderate to moderately severe pain. It has two complementary mechanisms of action: it binds with low affinity to μ -opioid receptors and inhibits reuptake of norepinephrine and serotonin. Analgesic action is only partially reversed by μ -opioid receptor blockade with naloxone.⁷¹ This indicates that tramadol's effect likely is not governed primarily through μ -opioid receptors but, rather, may depend on the combination of its two mechanisms of action, per-

haps in a synergistic fashion.⁷² Tramadol, thus, is a nonscheduled drug, and the serious side effects typically associated with opioids—such as dependence,⁷³ sedation, respiratory depression⁷⁴ and constipation—occur less frequently with it.^{66,74} The side effects commonly seen with tramadol include nausea, dizziness, drowsiness and tiredness.⁷⁵ Tramadol also has a low rate of abuse, approximately one case per 100,000 patients.⁷⁶ However, tramadol is not recommended for use in patients who have a history of drug dependence or abuse.⁷⁷ The risk of seizures seen with concomitant administration of certain drugs—such as monoamine oxidase inhibitors or selective serotonin reuptake inhibitors—is low,^{78,79} and adherence to dosage guidelines appears to decrease the seizure risk.⁶⁶

The significance of tramadol's lack of sedation is particularly crucial for same-day dental surgery. Tramadol also is not associated with the same adverse event profile of either NSAIDs or traditional opioids.⁷³ Adverse events following a single dose of tramadol include nausea, dizziness and vomiting, but these effects generally are mild and transient. Importantly, tramadol does not appear to have the ceiling dose effect common to many other analgesics. McQuay and Moore²⁶ reviewed 18 studies which demonstrated that all doses of tramadol were superior to placebo in relieving postsurgical and dental pain and showed a dose-response effect. For instance, in one study they reviewed,⁸⁰ tramadol 200 mg was more effective than 100 mg after third-molar extraction.

There are several meta-analyses showing the efficacy of tramadol in outpatient or day surgeries. For example, tramadol 50, 100 and 150 mg provided significantly more analgesia than placebo as determined by single-patient data meta-analysis, and also has been shown by single-patient data meta-analysis to have analgesic efficacy equal to that of aspirin 650 mg plus codeine 60 mg.⁸¹ Unlike aspirin, acetaminophen and codeine, which have an analgesic duration of approximately four hours, tramadol provides analgesia for five to six hours after dental surgery.^{8,9} Also, tramadol successfully managed pain for patients with chronic periodontitis, chronic pulpitis and alveolitis.⁸²

Benzodiazepines. Benzodiazepines are

Codeine alone has not been found as effective as other common analgesics for relief of postextraction pain.

increasingly being used acutely to decrease patient anxiety. Their sedative, anxiolytic and amnesic properties, along with their low risk of creating respiratory depression, are especially relevant for outpatient dental procedures.⁸³ Midazolam's ability to decrease postoperative anxiety scores and provide complete surgical amnesia (lasting about 25 minutes) was demonstrated in a pilot study in which intravenous midazolam was added to local anesthetic in third-molar extraction.⁸⁴ In another study, midazolam decreased anxiety compared with placebo in healthy young adults, but the addition of fentanyl to parenteral midazolam added the opioid-related side effect of transient respiratory depression. A multidrug combination of fentanyl, midazolam and methohexital provided somewhat better analgesia but produced deeper sedation.⁸⁵

Treatment of anxiety related to dental procedures can be a major concern with pediatric patients. Extreme preoperative anxiety may prolong induction of anesthesia and lead to postoperative negative effects. Oral midazolam has been shown to produce significant anterograde amnesia in children when given as early as 10 minutes before a surgical procedure.⁸⁶ A pilot study suggested that oral midazolam may be useful for conscious sedation in uncooperative pediatric dental patients.⁸⁷ Increasing oral doses of another benzodiazepine, alprazolam, produced decreased anxiety during oral surgery, but was associated with memory impairment.⁸⁸ The ability to use the oral route of administration is especially important in children. In a clinical trial in children undergoing multiple dental extractions, oral tramadol added to anxiolytic premedication with oral midazolam provided effective postextraction analgesia.⁸⁸

Another benzodiazepine, diazepam, may be useful in some patients for treatment of conditions associated with muscle spasm and pain. However, its long-term use is limited by sedation, abuse potential and dependence potential. Diazepam may have additive side effects with other central nervous system depressants.⁸⁹

Benzodiazepines may exhibit an adverse synergy with opioids in terms of their sedation, respiratory and blood pressure-lowering effects. Combinations of benzodiazepine and opioids are used

widely for conscious sedation but are associated with significant risks from coadministration. It has been recommended that these combinations be used only under conditions in which adequate cardiopulmonary monitoring, supplemental oxygen and resuscitative equipment, and trained personnel are immediately available.⁶⁷

COMBINATION ANALGESIC THERAPY FOR POSTOPERATIVE DENTAL PAIN

Analgesic monotherapy has shown equivocal success in treating dental pain. The goal of combining analgesics with different mechanisms of action is to use lower doses of the component drugs, thereby improving analgesia without increasing adverse effects. This can be achieved by targeting different pain pathways simultaneously⁹⁰ and increasing range of action by combining a fast-onset, short-acting analgesic (such as acetaminophen) for milder pain with a slower-onset, longer-duration analgesic (such as codeine or tramadol) for more severe pain. Also, when used in combination, the additive and synergistic effects of different analgesics may allow for lower doses.^{72,91}

Ceiling effect. The ceiling effect helps explain why combination therapy can be useful with acetaminophen and NSAIDs. Even after administration of clinically recommended doses, some patients will require additional analgesic therapy.⁹² Because of the ceiling effect (indicated by the relatively flat part of the dose-response curve), further increases in the dose of acetaminophen or NSAID beyond a certain point will produce minimal increase in analgesic effect but generally will increase side effects.⁹³ There is a ceiling dose for analgesia with NSAIDs, and higher dosing is required for an anti-inflammatory effect.⁴⁵

The ceiling effect also can explain how toxicity may occur, particularly with the use of over-the-counter acetaminophen or NSAID preparations. Patients frequently are unaware of the risks of taking increased doses of medication and consider only the potential benefits of increased effectiveness.⁹⁴ The reasoning is that if one tablet of a drug has an inadequate effect, then taking two or more tablets should achieve a twofold or greater

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Treatment of anxiety related to dental procedures can be a major concern with pediatric patients. Extreme preoperative anxiety may prolong induction of anesthesia and lead to postoperative negative effects.

response, thereby providing sufficient therapeutic effect. But, because of the ceiling effect, the expected increased pain relief does not occur and toxicity may result. More is not necessarily better.⁴⁵

Acetaminophen inadvertently may be administered concomitantly with another preparation containing acetaminophen, so clinicians need to educate patients about the potential risk of taking too many acetaminophen products.⁹⁵ Although significant side effects are rare when acetaminophen is taken at therapeutic doses, acute toxic doses of more than 100 mg/kilograms in adults and 150 mg/kg in children can cause hepatotoxicity.⁹⁶

A ceiling effect may sometimes be seen for side effects. For example, at low doses, there is a dose-response relationship for respiratory depression with certain opioids. But, at higher doses, no additional respiratory depression may occur. However, the “ceiling” for respiratory depression may be higher than the typical analgesic doses.⁶⁷

Traditionally, a therapeutic dose of a nonopioid has been used to achieve maximal possible analgesia through one mechanism of action when it is combined with the minimal dose of opioid that provides additive analgesia without unacceptably increasing side effects.⁹³

Clinical trials using combinations of acetaminophen or an NSAID with an opioid or tramadol in dentistry have been reported,^{25,29,48,92,93,100,102} but no studies have been published to date using a COX-2 NSAID with an opioid or tramadol for pain related to dental procedures.

Acetaminophen combinations. Acetaminophen is an effective analgesic for mild pain, but to manage more severe pain it typically is combined with codeine or one of its derivatives.^{26,81,97-99} Opioid and acetaminophen combination studies^{25,29,48,92,93,99,100} show that a combination is better than opioids or acetaminophen alone.⁹⁹ Analgesic advantages for oral surgery are optimal with acetaminophen 1,000 mg^{25,28,29,100} combined with codeine 60 mg^{28,29,100} or a codeine derivative such as oxycodone 10 mg with acetaminophen 1,000 mg²⁵ if the pain is more severe. Acetaminophen 650 mg plus oxycodone 10 mg has been shown to be effective compared

with placebo in managing postoperative dental pain.¹⁰¹ An acetaminophen dose as low as 500 mg combined with oxycodone 5 mg is more efficacious in the treatment of dental pain than is either drug alone.²⁵ The combination of acetaminophen 650 mg and codeine 30 mg was slightly more effective than acetaminophen alone as determined by pain intensity difference and pain relief scores.¹⁶ Other studies have combined acetaminophen 500 mg with hydrocodone 5 mg or acetaminophen 300 mg with codeine 30 mg and demonstrated analgesia better or equal to placebo, but found no difference between the two combinations for the treatment of pain related to third-molar extraction surgery.¹⁰² While acetaminophen 300 mg plus codeine 30 mg was not significantly more effective than placebo for TOTPAR and peak pain relief, overall evaluation and total anxiety control was significantly better

for the combination drug.¹⁰³ However, a higher dose of hydrocodone, such as 7.5 mg, combined with acetaminophen 500 mg had slightly more analgesic efficacy than did codeine 30 mg plus acetaminophen 300 mg, and both were better than placebo for oral surgery.¹⁰⁴ Both treatments resulted in analgesia that began 30 minutes after administration of the drug and continued for five hours.¹⁰⁴

Since tramadol 150 mg alone has been shown to have better efficacy overall than the combination of propoxyphene 65 mg and acetaminophen 650 mg,²⁶ as well as propoxyphene alone,¹⁰⁵ the combination of acetaminophen and tramadol would be expected to provide greater analgesia than the combination of acetaminophen and propoxyphene. In a study involving 1,197 patients with moderate-to-severe dental pain following extraction of two or more third molars, the combination of tramadol 75 mg with acetaminophen 650 mg provided more effective, rapid and long-acting pain relief than did tramadol or acetaminophen alone.¹⁹ The estimated time to onset of action for tramadol plus acetaminophen was 17 minutes (vs. 51 minutes for tramadol and 18 minutes for acetaminophen) and the duration of action (time to remedication) was 5.0 hours (vs. 2.0 hours for tramadol and 3.1 hours for acetaminophen). The tramadol and acetaminophen combination also has demonstrated efficacy for other types of pain, including

Acetaminophen is an effective analgesic for mild pain, but to manage more severe pain it typically is combined with codeine or one of its derivatives.

low back pain and osteoarthritis.¹⁰⁶

NSAID combinations. Similar to acetaminophen, NSAIDs have a ceiling effect and therefore should be combined with other analgesics for total pain relief after major surgery.¹⁰⁷ NSAIDs also allow for a significant dose reduction of opioids and hence can be useful in minimizing opioid side effects.¹² Opioids such as codeine, hydrocodone and oxycodone typically are combined with aspirin or ibuprofen to manage acute dental pain.⁴³ The combination of ibuprofen 400 mg and codeine 60 mg is superior to ibuprofen 400 mg alone as determined by a meta-analysis of randomized controlled clinical studies (including studies of dental pain).⁴⁸ Ibuprofen 400 mg and oxycodone 10 mg provided a faster onset of relief from dental pain than did ibuprofen 400 mg alone.⁹³ The combination of ibuprofen with 2.5 or 5 mg of oxycodone was not significantly different from ibuprofen alone in providing pain relief.⁹³ The combination of hydrocodone 15 mg combined with ibuprofen 400 mg was superior to ibuprofen 400 mg alone for all hourly measurements of analgesia after abdominal surgery, and side effects were associated primarily with the GI and central nervous systems.¹⁰⁸ The combination of ibuprofen 400 mg with hydrocodone 15 mg was superior to the combination of acetaminophen 600 mg with codeine 60 mg in providing analgesia after third-molar extraction, as demonstrated by superior total analgesic effect, duration of analgesia and global evaluation.¹⁰⁹

Tramadol has been shown to be effective at managing dental pain when combined with a peripherally acting NSAID. Combining tramadol 100 mg with the NSAID flurbiprofen (100 mg) significantly reduced pain vs. placebo at six hours and 24 hours following pulpectomy (a weak analgesic model); neither tramadol nor flurbiprofen significantly relieved pain vs. placebo at six and 24 hours when used as monotherapy.⁹² This is an important therapeutic finding for the management of endodontic pain, since NSAIDs have a ceiling dose and some patients may require analgesia beyond the recommended dose. Tramadol and diclofenac have been shown to be effective in pain management by some researchers,¹¹⁰ while no added effect was found by others.¹¹¹ Tramadol plus ibuprofen increased the efficacy of pain relief in patients with various types of dental pain.⁸² Importantly, tramadol has been shown in clinical trials to allow for dose-sparing with ibuprofen¹¹² and naproxen.¹¹³

CONCLUSIONS

Most of the monotherapeutic options for postoperative dental pain have limitations. Acetaminophen is effective and safe for mild pain, but often is inadequate for more severe pain after dental surgery and has demonstrated a ceiling effect at 1,000 mg. Tramadol and traditional opioids typically are effective for more severe pain, although they can have limited efficacy as monotherapy after dental surgery. NSAIDs are effective for inflammatory pain and generally are well-tolerated, but they carry potentially serious GI, cardiac and renal toxicities and also have a ceiling effect.

The differing mechanisms of action of these drugs allows for improved analgesia when they are used in combination, even at reduced doses. Combination analgesic therapy can increase the efficacy of dental pain management and reduce side effects, minimizing pain and reducing recovery time. Several studies of opioid/acetaminophen combinations and traditional NSAID/opioid combinations have demonstrated their effectiveness for acute dental pain. Early studies using tramadol in combination with acetaminophen or NSAIDs suggested that these combinations are effective. Additional studies are needed to evaluate the efficacy and safety of the newer, safer agents (tramadol and COX-2 inhibitors) in combination with acetaminophen or each other, to determine if these combinations enhance relief of acute moderate-to-severe pain without the typical adverse-effect profile of NSAIDs or opioids. ■

Dr. Mehlisch is president, Donald R. Mehlisch, M.D., D.D.S., & Associates, 4004 Harborlight Cove, Austin, Texas 78731-5134, e-mail "dmehlisch@aol.com". Address reprint requests to Dr. Mehlisch.

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