Combining ibuprofen and acetaminophen for acute pain management after third-molar extractions

Translating clinical research to dental practice

Paul A. Moore, DMD, PhD, MPH; Elliot V. Hersh, DMD, MS, PhD

ABSTRACT

Background. Effective and safe drug therapy for the management of acute postoperative pain has relied on orally administered analgesics such as ibuprofen, naproxen and acetaminophen, or *N*-acetyl-*p*-aminophenol (APAP), as well as combination formulations containing opioids such as hydrocodone with APAP. The combination of ibuprofen and APAP has been advocated in the last few years as an alternative therapy for postoperative pain management. The authors conducted a critical analysis to evaluate the scientific evidence for using the ibuprofen-APAP combination and propose clinical treatment recommendations for its use in managing acute postoperative pain in dentistry.

Types of Studies Reviewed. The authors used quantitative evidence-based reviews published by the Cochrane Collaboration to determine the relative analgesic efficacy and safety of combining ibuprofen and APAP. They found additional articles by searching the Ovid MEDLINE, PubMed and ClinicalTrials.gov databases.

Conclusions. The results of the quantitative systematic reviews indicated that the ibuprofen-APAP combination may be a more effective analgesic, with fewer untoward effects, than are many of the currently available opioid-containing formulations. In addition, the authors found several randomized controlled trials that also indicated that the ibuprofen-APAP combination provided greater pain relief than did ibuprofen or APAP alone after third-molar extractions. The adverse effects associated with the combination were similar to those of the individual component drugs.

Practical Implications. Combining ibuprofen with APAP provides dentists with an additional therapeutic strategy for managing acute postoperative dental pain. This combination has been reported to provide greater analgesia without significantly increasing the adverse effects that often are associated with opioid-containing analgesic combinations. When making stepwise recommendations for the management of acute postoperative dental pain, dentists should consider including ibuprofen-APAP combination therapy.

Key Words. Ibuprofen; acetaminophen; analgesics; drug combinations; practice guidelines.

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The strategy of combining two analgesic agents having distinct mechanisms or sites of action, such as combining a peripherally acting analgesic with a centrally acting analgesic, has been advocated for many years.[1-4] A common example is the analgesic formulation containing acetaminophen, or *N*-acetyl-*p*-aminophenol (APAP), combined with the opioid hydrocodone (for example, Vicodin [Abbott Laboratories, Abbott Park, Ill.] or Lorcet [UCB, Atlanta]). This combination is the most frequently prescribed drug in the United States.[5] Analgesic formulations containing an opioid and a peripherally acting analgesic consistently provide greater pain relief than do the component agents when administered alone.[3,4,6-9] In a Cochrane systematic review of 20 high-quality clinical trials, investigators also confirmed the additive pain relief that occurs when combining the opioid oxycodone with APAP.[10]

Including an opioid as part of an analgesic combination formulation, however, increases the risk of patients' experiencing adverse effects such as nausea, vomiting and psychomotor impairment; restricts the use of central nervous system depressants; and carries significant risk of experiencing drug misuse

Dr. Moore is a professor of pharmacology and dental public health, and the chair, Department of Dental Anesthesiology, School of Dental Medicine, University of Pittsburgh, Pittsburgh, Pa. 15261, e-mail pam7@pitt.edu. Address reprint requests to Dr. Moore.
Dr. Hersh is a professor of pharmacology, Department of Oral Surgery and Pharmacology, School of Dental Medicine, University of Pennsylvania, Philadelphia.

and abuse.[2,3,11,12] Alternative combination analgesics that do not contain opioids have been advocated as a means for avoiding the potential adverse reactions associated with opioids. Combinations of diclofenac or ketoprofen and APAP have been evaluated, and investigators have advocated their use for many years.[13,14] An example of a fixed-dose analgesic combination that does not contain an opioid is the formulation of ibuprofen with APAP (Maxigesic) that has been marketed within the past five years in New Zealand by AFT Pharmaceuticals (Auckland, New Zealand).[15]

PHARMACOLOGY OF IBUPROFEN AND ACETAMINOPHEN

Ibuprofen in unit doses of 200 milligrams is a common over-the-counter (OTC) analgesic marketed as Advil (Pfizer, New York City) and Motrin IB (McNeil-PPC, Morris Plains, N.J.) as well as several generic products. Prescription-strength ibuprofen also is available in unit doses of 400 mg, 600 mg and 800 mg. In a survey published in 2006, investigators found that ibuprofen was the most frequently recommended nonprescription peripherally acting analgesic among oral and maxillofacial surgeons for the management of postoperative pain after third-molar extractions in the United States.[16] Ibuprofen and the other analgesics classified as nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) are safe and effective for treating mild to moderately severe postoperative pain and inflammation.[11,17,18] Investigators in a Cochrane systematic review of 72 clinical studies in which authors compared ibuprofen and a placebo found that 200 mg and 400 mg of ibuprofen were effective analgesics.[19] They also found adverse events for ibuprofen were uncommon and similar to those of the placebo. Randomized controlled trials (RCTs) in which investigators evaluated higher doses of ibuprofen are limited in terms of number. Doses of ibuprofen that were greater than 600 mg appeared to provide little additional analgesia, but they might be useful in decreasing inflammation in rheumatoid diseases.[20,21]

The analgesic mechanism of action common to ibuprofen and the other NSAIDs is their capacity to limit the hyperalgesia associated with tissue trauma by competing with arachidonic acid for cyclooxygenase (COX) enzymes, thereby blocking the synthesis of inflammatory and hyperalgesic prostaglandins within peripheral tissues.[2,11,22] The results of an animal study suggest that a reduction of central prostaglandin production by NSAIDs, including ibuprofen, also contributes to their analgesic action.[23]

APAP is an effective and commonly recommended analgesic medication that has antipyretic activity but little anti-inflammatory activity.[11] Available as an OTC medication, APAP is marketed under the brand name of Tylenol (McNeil-PPC) and various generic formulations. The popularity of APAP has been attributed to its relative safety and efficacy.[11,17] In a Cochrane systematic review of 51 RCTs rated as high quality, a single dose of APAP (500 mg or 1,000 mg) consistently provided effective postoperative pain relief for about four hours and was associated with few adverse events.[24]

Although APAP is an effective analgesic for postoperative pain after third-molar surgery,[25,26] it may not be as effective as a full therapeutic dose of ibuprofen (that is, 400-600 mg) or other NSAIDs.[2,14,18,27,28] It is well tolerated by most patients and has few adverse drug interactions.[3,29,30] Other than reported allergic reactions, there are few contraindications for its use.[3,24]

In contrast to ibuprofen and other NSAIDs, APAP has limited anti-inflammatory activity and minimally inhibits platelet aggregation.[17,24] Although several mechanisms of action have been proposed for APAP's selective analgesic activity, none have been confirmed. Investigators of APAP analgesic activity generally conclude that multiple mechanisms may be involved.[31] Elucidation of APAP's activity is complicated because it appears that APAP may have an active metabolite, and findings in animal studies sometimes are difficult to confirm in humans.[31-33] Previously proposed mechanisms for APAP's analgesic effects include an interaction with a COX-1 variant, activation of the opioidergic and cannabinoid systems, and an activation of descending serotonergic analgesic pathways.[31-35] Investigators indicate that APAP may act as a reducing agent capable of inactivating COX activity.[36-38] Unlike traditional NSAIDs that compete with arachidonic acid during the initial enzymatic cascade that synthesizes prostaglandins, APAP may function by inactivating the COX enzymes responsible for the final catalytic reaction.[31,36-38] Conceivably, a combination of an NSAID and APAP may provide greater overall inhibition of COX enzymes by acting at two different sites, thereby providing greater analgesic activity. Additional additive analgesic

ABBREVIATION KEY. APAP: Acetaminophen, or *N*-acetyl-*p*-aminophenol. **COX:** Cyclooxygenase. **FDA:** Food and Drug Administration. **NNT:** Number needed to treat. **NSAID:** Nonsteroidal anti-inflammatory drug. **OTC:** Over the counter. **prn:** As needed. **q:** Every. **RCT:** Randomized controlled trial.

action also could be explained by the COX-inhibitory activity of ibuprofen and non–COX-related mechanisms of APAP.

Both APAP and ibuprofen are indicated for the management of mild and moderate pain.[18] Their utility when used as the sole analgesic (monotherapy) for managing severe pain appears to be limited owing to potential toxicity and an apparent ceiling effect seen at high dosages.[11,20]

RATIONALE FOR ANALGESIC COMBINATIONS

Orally administered analgesics are the primary drug therapy used to manage acute postoperative pain in dentistry. Because monotherapy often provides inadequate pain relief, investigators have advocated combinations of two or more analgesic drugs.[1,2,4,39]

Beaver[40] proposed six potential advantages of formulating drug combinations when treating acute pain: improve analgesic efficacy, decrease adverse reactions, lower costs, treat disorders having multiple symptoms, improve patient adherence and facilitate absorption. The most valuable advantage for combining ibuprofen and APAP is the potential to improve analgesic efficacy without increasing the incidence of adverse drug reactions..

There are four possible mechanisms that might explain why a combination of analgesic drugs might improve pain relief. The first is that there may be additive effects when using two analgesic agents that have different mechanisms.[39,41] As investigators in a Cochrane systematic review reported, the commonly prescribed fixed-dose formulations containing an opioid (oxycodone) combined with a peripherally acting analgesic (APAP) have consistently demonstrated this additive analgesic effect.[10] A 2011 report of the most frequently prescribed drugs in the United States ranked 10 analgesic agents in the Top 200.[5] Three of these analgesics were formulations containing APAP combined with the opioid analgesics hydrocodone, oxycodone and codeine. These three combinations ranked as the first, 45th and 138th most frequently prescribed, respectively. Among practicing oral and maxillofacial surgeons in the United States in 2006, the most frequently recommended prescription analgesics for managing pain after third-molar extractions were APAP-hydrocodone (for example, Vicodin) and APAP-oxycodone (for example, Percocet [Endo Pharmaceuticals, Malvern, Pa.]).[16]

A second possible mechanism for improved analgesia is the unlikely possibility that one of the agents alters the pharmacokinetics of the other, resulting in higher plasma concentrations and greater efficacy. An assessment of potential ibuprofen and APAP pharmacokinetic drug interactions was published in 2010.[42] The authors concluded that there were no apparent differences in calculated pharmacokinetic parameters (clearance, volume of distribution, absorption half-life, maximum concentration and time to maximum concentration) between the components administered alone and the ibuprofen-APAP combination.

A third possible mechanism for improved analgesia with analgesic combinations is that one agent alters the nociceptive sensitivity of the other agent. For example, after administration of an NSAID, expression of an altered form of COX enzymes may occur, and this alteration has greater sensitivity to APAP.[43] Augmenting sensitivity could explain a supra-additive (synergistic) drug interaction.

Genetic differences among patients is the fourth possible mechanism to explain greater analgesia when administering a combination of analgesics. Genetic variations in sensitivity or metabolism may result in a patient's having a better response to one agent than to another.[43,44] Genetic polymorphisms may result in some patients' not having the specific metabolic enzymes required when administering prodrugs such as many of the opioids.[45-48] In addition to a combination of two analgesics providing additive analgesic effects, there is a greater likelihood that at least one of the agents will provide pain relief. This pharmacological concept has been described as "cross-firing" (or the more popular term today, "multimodal analgesia") and justifies the use of oral analgesic formulations containing an opioid, such as hydrocodone in combination with APAP.[39,40,49]

Until as recently as 2010, the number of published clinical trials in which investigators evaluated the additive analgesic efficacy when APAP was combined with any of the NSAIDs were limited and varied greatly regarding the NSAIDs selected, the severity of pain and the types of surgery.[13,14,50-52] An early example of an APAP-NSAID combination is aspirin combined with APAP.[53] This combination usually is not recommended for postoperative pain management in dentistry because of aspirin's known ability to inhibit platelet aggregation and the potential for increased postoperative bleeding and ecchymosis after surgery.[54,55] Investigators in studies regarding this combination generally have not seen an added benefit in pain relief when they compared it with the maximum doses of either agent alone.[49,53] In addition, there is

little indication that the lower doses of aspirin and APAP used in this combination decrease the incidence of adverse effects.[17]

Investigators in two studies evaluated the added pain relief associated with a combination of the NSAID diclofenac and APAP.[13,51] For example, Breivik and colleagues[51] evaluated the analgesic efficacy of a combination of diclofenac 100 mg and APAP 1,000 mg in a group of 120 patients undergoing third-molar extractions. Diclofenac 100 mg is an NSAID commonly prescribed in Europe, and it is approximately equivalent to a dose of 800 mg of ibuprofen.[11] Investigators evaluated analgesic efficacy for eight hours after participants underwent third-molar extractions by recording pain intensity by using a visual analog scale and pain relief by using a categorical pain scale. Participants who received the combination of diclofenac and APAP had significantly less pain than did those who received the individual components (100 mg of diclofenac or 1,000 mg of APAP) or a combination of APAP and codeine. Compared with the nonopioid analgesics diclofenac, APAP and the diclofenac-APAP combination, the combination containing codeine led to adverse drug reactions more frequently ($P = .037$).[51]

Similarly, the authors of a 2010 qualitative review reported the added benefit of APAP when used in combination with several NSAIDs, including ibuprofen, diclofenac, ketoprofen, ketorolac, aspirin, tenoxicam and rofecoxib.[52] The review included 21 human studies of postoperative pain relief experienced after different types of surgery. The conclusion of this review was that the combination of APAP and an NSAID may provide analgesia superior to that of either drug alone.

INFORMATION SUPPORTING IBUPROFEN-ACETAMINOPHEN COMBINATIONS IN DENTISTRY

To determine the clinical research evidence supporting the use of an ibuprofen-APAP analgesic drug combination, we sourced systematic, quantitative, evidence-based reviews published by the Cochrane Collaboration in which investigators assessed the efficacy and safety of NSAIDs, APAP and analgesic combinations when administered to manage postoperative dental pain. The authors of these quantitative systematic reviews assessed the quality of all available RCTs for a specific analgesic agent, conducted a meta-analysis and calculated a common statistic to allow for comparisons between analgesic agents. The calculated statistic the authors used for these reviews was number needed to treat (NNT), which has been defined as "the number of patients needed to be treated to obtain one additional patient achieving at least 50 percent maximum pain relief over four to six hours compared with placebo."[18] The lower the NNT, the more effective the analgesic drug therapy. In addition, we derived research reports that may have appeared in the literature since these systematic reviews were performed from Ovid MEDLINE, PubMed and Clinicaltrials.gov. Furthermore, we scrutinized the reference lists for published RCTs to ensure no recent clinical research studies were overlooked.

The Cochrane Database of Systematic Reviews contains 59 reviews categorized as "pharmacological treatments for anesthesia and pain control"; authors of 38 of these reviews evaluated single-dose oral analgesics for treatment of acute pain.[56] A published overview of these 38 systematic reviews included results specific to dental pain studies (primarily employing the third-molar extraction model).[18] Similarly, data from two large dental pain studies published in 2010 and 2011 in which investigators evaluated the analgesic efficacy of an ibuprofen-APAP combination[57,58] were used to calculate the combination's NNT.[44,59] We provide the relative analgesic efficacy for single-dose agents and combinations commonly used in dentistry on the basis of these calculated NNT values in Table 1.[10,18,44,59,60]

In addition to the two studies used to establish the NNT for the ibuprofen-APAP combination,[57,58] we identified through our search of the literature two additional RCTs in which investigators assessed the analgesic efficacy and safety of the combination after third-molar extractions.[42,61] The research design and description of these four studies in which investigators evaluated the ibuprofen-APAP combination are presented in Table 2[42,57,58,61] (page 903).

The authors of a study who compared the ibuprofen-APAP combination formulated with ibuprofen 300 mg and APAP 1,000 mg also evaluated it for pain management after third-molar extraction.[42] They administered analgesics preoperatively and every six hours for 48 hours postoperatively. They assessed pain intensity by using a 100-millimeter visual analog scale at four-hour intervals during the 48-hour postoperative evaluation. The authors found the group receiving the ibuprofen-APAP combination had significantly less pain than did either the group using ibuprofen alone ($P = .003$) or that using APAP alone ($P = .007$).[42]

Mehlisch and colleagues[57,58] conducted two separate studies in which they evaluated vari-

TABLE 1

Relative analgesic efficacy of oral analgesics.*

DRUG (DOSE, MILLIGRAMS)	NO. OF TRIALS	NO. OF PARTICIPANTS	NUMBER NEEDED TO TREAT (95% CONFIDENCE INTERVAL)†
Aspirin (600 or 650)	45	3,581	4.5 (4.0-5.2)
Aspirin (1,000)	4	436	4.2 (3.2-6.0)
APAP‡ (1,000)	19	2,157	3.2 (2.9-3.6)
Ibuprofen (200)	18	2,470	2.7 (2.5-3.0)
Celecoxib (400)	4	620	2.5 (2.2-2.9)
Ibuprofen (400)	49	5,428	2.3 (2.2-2.4)
Oxycodone (10) With APAP (650)	6	673	2.3 (2.0-6.4)
Codeine (60) With APAP (1,000)	26	2,295	2.2 (1.8-2.9)
Naproxen (500 or 550)	5	402	1.8 (1.6-2.1)
Ibuprofen (200) With APAP (500)	2	280	1.6 (1.4-1.8)

* All values were calculated from studies using a single dose of an oral analgesic after third-molar extraction.
† Data for number needed to treat were derived from several sources: Gaskell and colleagues,[10] Moore and colleagues[18,44] and Derry and colleagues.[59,60]
‡ APAP: Acetaminophen, or *N*-acetyl-*p*-aminophenol.

ous doses of ibuprofen and APAP, alone and in combination. Other investigators used the data from these two studies to establish the NNT for the ibuprofen-APAP combination in Table 1.[59] In the first study, the authors evaluated the sum of pain relief ratings and pain intensity difference ratings hourly for eight hours in 234 participants undergoing third-molar extractions.[57] Participants who received the higher-dose combination of 400 mg of ibuprofen with 1,000 mg of APAP had significantly better pain relief during the eight-hour study than did participants receiving the individual components (either 400 mg of ibuprofen alone or 1,000 mg of APAP alone; P =.001), participants receiving the lower-dose combination of 200 mg of ibuprofen with 500 mg of APAP (P = .02), or participants receiving a placebo (P = .001). As illustrated in Figure 1 (page 904),[57] the lower-dose combination provided less relief than did the higher-dose combination, but it provided better pain relief than did 1,000 mg of APAP (P = .03).[57] In addition, 400 mg of ibuprofen was not significantly better than 1,000 mg of APAP.

In a large follow-up study, Mehlisch and colleagues[58] again evaluated analgesic efficacy among 715 participants for eight hours by using the third-molar extraction pain model. In this analgesic trial, they compared three fixed-dose combinations of ibuprofen plus APAP with each of the component analgesics and placebo. Participants who received the highest dose combination of 400 mg of ibuprofen with 1,000 mg of APAP had significantly better pain relief than did those who received the individual components (400 mg of ibuprofen, P = .047; 1,000 mg of APAP, P = .001). The middle dose combination of 200 mg of ibuprofen with 500 mg of APAP also provided significantly better pain relief than did the individual components (200 mg of ibuprofen, P = .001; 500 mg of APAP, P = .001). The lowest dose combination of 100 mg of ibuprofen with 250 mg of APAP provided less relief than did the higher-dose combinations and provided pain relief better only than the placebo (P = .001). Treatment-related adverse drug reactions were less frequent with the combination therapies than with the equivalent dose of the individual monotherapy (P < .05).[58]

Daniels and colleagues[61] conducted another recent assessment of an ibuprofen-APAP combination.In their comprehensive clinical trial, they enrolled 678 participants to compare a placebo and four combination therapies: 400 mg of ibuprofen with 1,000 mg of APAP, 200 mg of ibuprofen with 500 mg of APAP, 1,000 mg of APAP with 30 mg of codeine and 400 mg of ibuprofen with 25.6 mg of codeine (Figure 2,[10,18,44,59,60] page 905). They evaluated analgesic efficacy after participants underwent third-molar extractions by using categorical scales of pain relief and pain intensity. Participants who received the higher-dose combination of 400 mg of ibuprofen with 1,000 mg of APAP had significantly less pain than did those receiving the ibuprofen-codeine combination (P = .0001), the APAP with codeine combination (P < .0001) or placebo (P < .0001). The lower-dose combination of 200 mg of ibuprofen with 500 mg of APAP provided less relief than did the higher dose of 400 mg of ibuprofen with 1,000 mg of APAP combination (P = .0005), but it provided more relief than did the APAP with codeine comparator (P = .0001).[61] In addition, 400 mg of ibuprofen with 25.6 mg of codeine was not significantly different from 200 mg of ibuprofen with 500 mg of APAP. The overall incidence of adverse reactions included nausea (26.7 percent), vomiting (19.5 percent), headache (14.9 percent), dizziness (9.9 percent),

alveolar osteitis (3.7 percent) and temperature increase (2.7 percent). Treatment-emergent adverse events were more frequent with the combinations containing ibuprofen and codeine (34.9 percent) or APAP and codeine (39.8 percent) than were treatment-emergent adverse events for the combinations containing 400 mg of ibuprofen with 1,000 mg of APAP (24.9 percent) or for the combinations containing 200 mg of ibuprofen with 500 mg of APAP (18.5 percent).[61]

Investigators incorporated a secondary analysis derived from two of these randomized, double-masked, placebo controlled studies[57,58] into previously published Cochrane meta-analyses[18,19] to provide confirmation of the relative efficacy of the ibuprofen-APAP combination.[44] They extracted comparative data available for participants receiving the 200 mg of ibuprofen with 500 mg of APAP combination and used them to calculate an NNT for the combination (1.6; 95 percent confidence interval, 1.4-1.8).[44] Table 1 delineates this and other published NNT values calculated within Cochrane reviews for single-agent analgesics[18] and opioid combinations.[9,10,62] The lowest NNT was for the ibuprofen-APAP combination therapy (Table 1[10,18,44,59,60]). Participants receiving the ibuprofen-APAP combination were less likely to request rescue analgesics (up to eight hours) than were participants receiving ibuprofen or APAP alone.[19,44] Care must be taken when interpreting this calculation because of the relatively small number of patients evaluated (n = 280) compared with the numbers for the other treatments we analyzed. However, the results of several clinical trials regarding dental pain that we did not include in this secondary analysis[43,61,63] also support the conclusion that the combination of ibuprofen and APAP is a more effective analgesic than either agent alone.

TABLE 2

Clinical research assessing ibuprofen-APAP* combinations for analgesia in dentistry.

AUTHOR, YEAR	NO. OF PARTICIAPNTS (AGE, YEARS)	COMBINATION (DOSE, MILLIGRAMS)	COMPARATORS (DOSE, mg)
Merry and Colleagues,[42] 2010	135 (16-40)	Ibuprofen (300) with APAP (1,000)	Ibuprofen (300)
			APAP (1,000)
Mehlisch and Colleagues,[57] 2010	234 (20.8)	Ibuprofen (400) with APAP (1,000)	Ibuprofen (400)
			APAP (1,000)
			Placebo
		Ibuprofen (200) with APAP (500)	
Mehlisch and Colleagues,[58] 2010	715 (20.3)	Ibuprofen (400) with APAP (1,000)	Ibuprofen (200)
		Ibuprofen (200) with APAP (500)	Ibuprofen (400)
		Ibuprofen (100) with APAP (250)	APAP (500)
			APAP (1,000)
			Placebo
Daniels and Colleagues,[61] 2011	678 (20.0)	Ibuprofen (400) with APAP (1,000)	Ibuprofen (400)/ codeine (25.6)
		Ibuprofen (200) with APAP (500)	APAP (1,000)/ codeine (30)
			Placebo

* APAP: Acetaminophen, or *N*-acetyl-*p*-aminophenol.

THERAPEUTIC STRATEGIES FOR IBUPROFEN-ACETAMINOPHEN ANALGESIA

The results of available clinical trials demonstrated a therapeutic advantage for the combined use of NSAIDs with APAP generally and ibuprofen with APAP specifically.[52] Applying these clinical research findings to dental practice, however, requires some precaution.

Dose selection. The research findings indicate that the additive effects of the ibuprofen-APAP combination are seen with use of many different dosing strategies. When recommending the ibuprofen-APAP combination, the specific dose of ibuprofen-APAP may be tailored to patient needs and the practitioner's expectations for postoperative pain. In the evaluation of ibuprofen alone for managing pain in patients who have undergone extraction of impacted third molars, the 400-mg dose appears to provide better analgesia than does the 200-mg dose.[19,64] Thus, for patients with moderate to severe pain, this full therapeutic dose of ibuprofen combined with APAP may be important for achieving the most effective analgesic response. Investigators in future studies are likely to give practitioners guidance regarding alternative NSAIDs and dosing strategies when administering analgesic combinations containing APAP.

Caution regarding APAP toxicity. The U.S. Food and Drug Administration (FDA) has alerted practitioners and consumers about potential liver toxicity associated with excessive use of APAP.[65] Acute liver failure caused by unintentional consumption of excessive amounts of APAP has been reported.[66] Toxicity induced

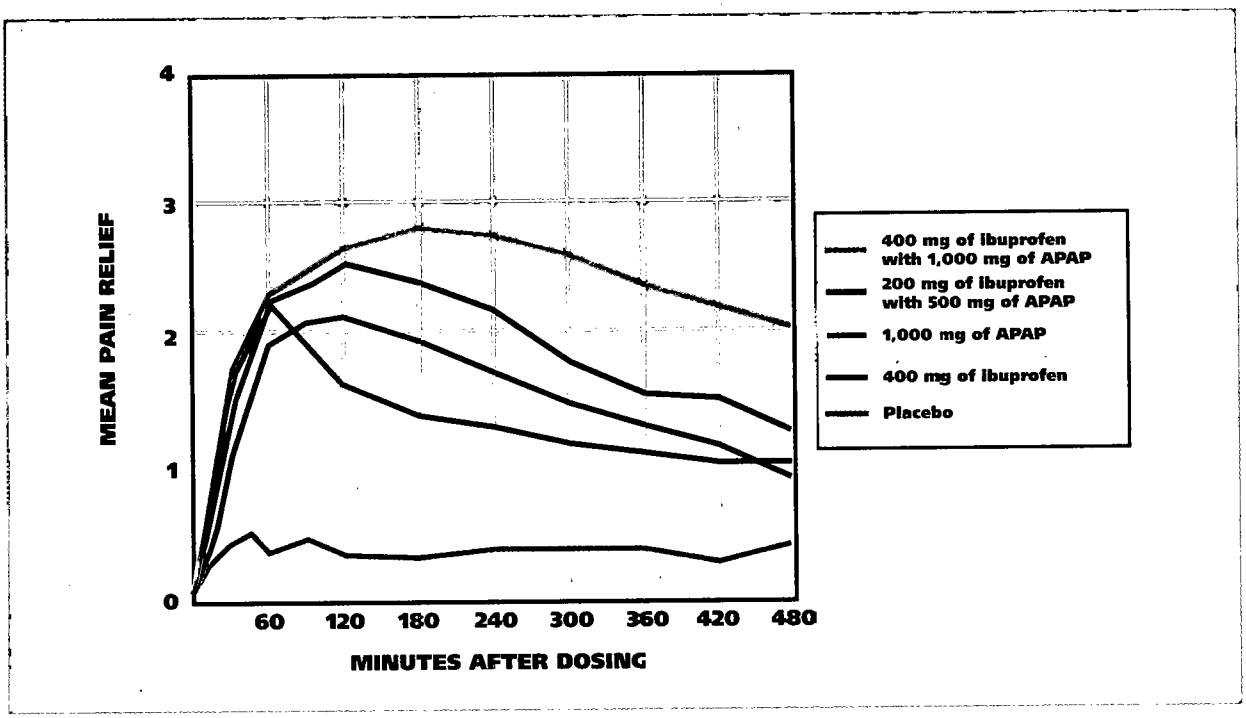

Figure 1. Pain relief of ibuprofen-acetaminophen combinations. Pain relief was recorded on a five-point scale, in which 0 indicated "none," 1 indicated "a little," 2 indicated "some," 3 indicated "a lot" and 4 indicated "complete." APAP: Acetaminophen, or *N*-acetyl-*p*-aminophenol. mg: Milligrams. Adapted with permission of Elsevier from Mehlisch and colleagues.[57]

by APAP has been reported when a daily dose of 4,000 mg is exceeded.[67] To prevent excessive consumption of APAP, the FDA has requested that the dose of APAP contained in prescription opioid-APAP analgesics be limited to a maximum of 325 mg.[68] Consequently, formulations that previously contained 750 mg of APAP and 7.5 mg of hydrocodone, such as Vicodin HP (Abbott Laboratories), have been reformulated to contain 300 mg of APAP and 7.5 mg of hydrocodone.[69]

When prescribing APAP for the management of acute postoperative pain, dentists must be careful to limit the dosing regimen to avoid potential overdose. Although a reduction in APAP's total daily dose has not been mandated by the FDA, continuing concerns about potential hepatic toxicity have resulted in McNeil-PPC, the manufacturer of Tylenol, voluntarily reducing its APAP daily dose recommendation from 4,000 to 3,000 mg.[70] Although a single dose of 1,000 mg of APAP may be tolerated, multiple daily doses of APAP should not exceed 500 mg every four hours or 650 mg every six hours. Dentists should warn patients to follow dosing instructions and inform them about how to avoid using many of the other OTC formulations that contain APAP.[67] In addition, if a rescue medication containing an opioid is believed to be warranted, an equally effective formulation containing ibuprofen instead of APAP (such as Vicoprofen [AbbVie, North Chicago, Ill.] or its generic equivalent) may be more appropriate.[71]

For use after procedures other than third-molar extractions. In dentistry, the additive effects of an ibuprofen-APAP combination have been studied most often by using the third-molar extraction pain model. This procedure frequently is performed in young adults who have no pre-existing infections or ongoing pain. After receiving endodontic therapy for pulpal necrosis, patients did not consistently report improved analgesia as has been reported by patients who have undergone third-molar extractions.[63,72] Patients having pain before treatment and severe postoperative pain may need alternative analgesic strategies that include opioids.[72-74]

The efficacies of APAP, ibuprofen and other NSAIDs differ depending on the surgical model being studied (for example, abdominal, gynecologic, orthopedic and dental).[14] Within dentistry, additional research evaluating postoperative pain management with this combination is needed for endodontic, periodontic and implant procedures.

Medical considerations. Although short-term use of ibuprofen and APAP are considered safe for most patients, the use of these agents,

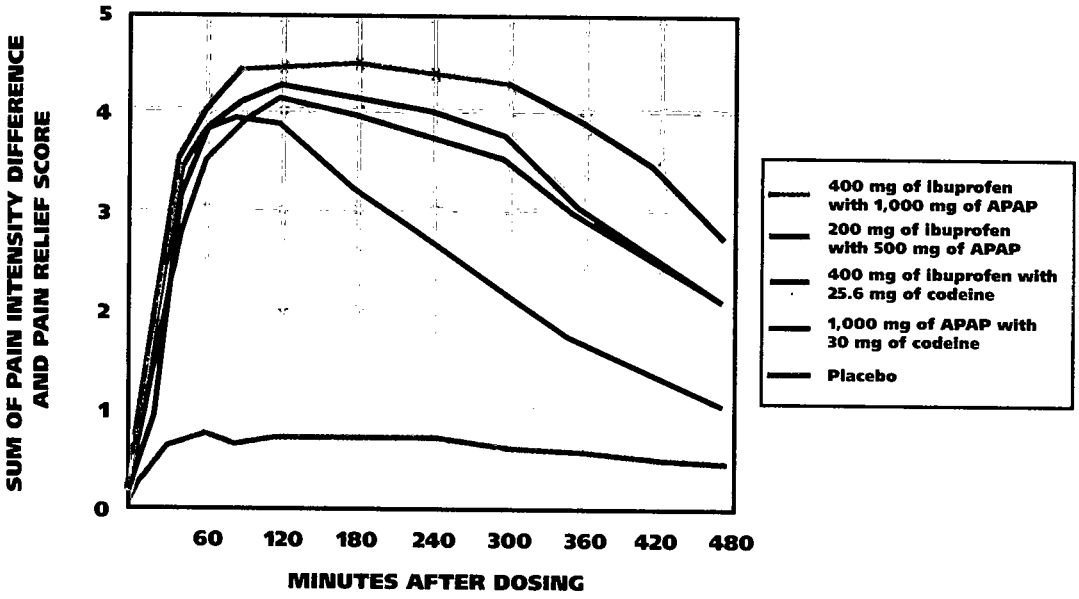

Figure 2. Ibuprofen-acetaminophen combinations versus codeine-nonopioid combinations. APAP: Acetaminophen, or *N*-acety.-*p*-aminophenol. mg: Milligrams. Adapted with permission of the International Association for the Study of Pain from Daniels and colleagues.[61]

either alone or in combination, may be contraindicated in those with certain medical histories. Administering ibuprofen or any of the NSAIDs to patients receiving warfarin or other anticoagulant medications may not be appropriate.[17] Patients who are regularly taking low-dose aspirin to prevent myocardial infarction should be advised to delay taking an NSAID for 30 to 60 minutes after taking aspirin because of the reported potential of the NSAID to interfere with the cardioprotective effect of low-dose aspirin.[75]

In addition, prolonged administration of APAP and ibuprofen has gastrointestinal and cardiovascular risks.[76] Because the mechanisms of the analgesic action of APAP and ibuprofen may be complementary, concern regarding the potential additive risks, particularly at high doses and with long-term administration of the combination, has been published.[37]

Limiting the need for opioid-containing analgesic combinations. The improved analgesic efficacy seen when the common OTC analgesics ibuprofen and APAP are combined may provide a therapeutic alternative to opioid-containing analgesics. Prescribers may find that routinely providing a prescription for Vicodin or Percocet is not necessary, and even if an opioid combination prescription is needed, fewer pills may be needed or a lower dose of opioid may be sufficient (for example, Vicodin instead of Vicodin HP). Table 1 indicates that the NNT for the combination of 10 mg of oxycodone and 650 mg of APAP (2.3) and the NNT for the combination of 60 mg of codeine and 1,000 mg of APAP (2.2) are not significantly better than the NNTs for 400 mg of ibuprofen (2.3), 500 mg of naproxen (1.8) or the combination of 200 mg of ibuprofen and 500 mg of APAP (1.6).[10,18,44,59,60] The demonstration that a combination of 200 mg of ibuprofen with 500 mg of APAP can provide equivalent analgesia after dental surgery without the adverse effects associated with opioid combinations may be clinically beneficial.[59] This nonopioid alternative to opioid-containing analgesics may be an effective strategy for preventing potential prescription drug abuse and diversion, which is a national concern associated with dispensing prescription drugs.[12,77]

Adjuncts to minimize postoperative discomfort. Prescribing oral analgesics after surgery should not be the sole strategy for postoperative pain control. Adjunctive pain control therapies can limit postoperative discomfort to an extent that severe pain is less likely. The use of the long-acting local anesthetic bupivacaine to provide extended soft-tissue and periosteal anesthesia is an effective strategy for limiting the need for oral analgesics.[78-80] The use of the corticosteroid dexamethasone is effective in limiting trismus, swelling and pain after third-molar surgery.[81-83] In addition, the use of peripherally acting analgesics such as ibuprofen or naproxen

TABLE 3

Stepwise guidelines for acute postoperative pain management in dentistry.

PAIN SEVERITY	ANALGESIC RECOMMENDATION*
Mild	Ibuprofen (200-400 milligrams) q† 4-6 hours: prn‡ for pain
Mild to Moderate	Ibuprofen (400-600 mg) q 6 hours: fixed interval for 24 hours Then ibuprofen (400 mg) q 4-6 hours: prn for pain
Moderate to Severe	Ibuprofen (400-600 mg) with APAP (500 mg) q 6 hours: fixed interval for 24 hours Then ibuprofen (400 mg) with APAP (500 mg) q 6 hours: prn for pain
Severe	Ibuprofen (400-600) with APAP (650 mg) with hydrocodone (10 mg) q 6 hours: fixed interval for 24-48 hours Then ibuprofen (400-600 mg) with APAP (500 mg) q 6 hours: prn for pain

* Additional considerations:
- Patients should be warned to avoid acetaminophen, or *N*-acetyl-*p*-aminophenol (APAP), in other medications. Maximum daily dose of APAP is 3,000 mg per day. To avoid potential APAP toxicity, a dentist should consider prescribing an opioid rescue medication containing ibuprofen.
- Maximum dose of ibuprofen is 2,400 mg per day. Higher maximal daily doses have been reported for osteoarthritis when under the direction of a physician.
- A decrease in postoperative pain severity has been demonstrated when a nonsteroidal anti-inflammatory drug is administered pre-emptively.[82]
- Long-acting local anesthetics can delay onset and severity of postoperative pain.[79,80]
- A perioperative corticosteroid (dexamethasone) may limit swelling and decrease postoperative discomfort after third-molar extractions.[81-83]

† q: Every.
‡ prn: As needed.

before surgery to pre-emptively manage postoperative sequelae decreases the severity and onset of acute postoperative pain.[26,83-85] Investigators have reported that all three of these strategies have been used by oral surgeons for pain management after third-molar extractions.[16]

CLINICAL RECOMMENDATIONS THAT INCLUDE IBUPROFEN-ACETAMINOPHEN COMBINATIONS

The demonstration of the improved analgesic efficacy of ibuprofen-APAP combinations compared with that of the component agents individually gives practitioners greater flexibility when selecting analgesic therapy for patients after they have undergone dental surgery.[62] Table 3 presents a stepwise and conservative approach to acute postoperative pain management for patients after third-molar surgery.[79-83] These recommendations provide valuable guidance for pain management when a practitioner has an expectation of mild, mild to moderate, moderate to severe or severe pain.

As with previous recommendations,[86] these stepwise guidelines recognize that NSAIDs are effective and remain the primary agent when treating most cases of postoperative dental pain. For patients who can tolerate NSAIDs, 200 to 400 mg of ibuprofen as needed for pain every four to six hours is recommended for mild pain. If this regimen provides inadequate pain relief, 400 to 600 mg of ibuprofen taken at the fixed interval of every six hours for the first 24 hours is recommended. If expected pain intensity is moderate to severe, a combination of 400 mg of ibuprofen with 500 mg of APAP taken every six hours is recommended. If severe postoperative pain is anticipated, 400 to 600 mg of ibuprofen plus an opioid-APAP combination equivalent of either 5 mg of hydrocodone with 325 mg of APAP or 10 mg of hydrocodone with 650 mg of APAP administered every six hours is recommended. The 650 mg of APAP dose combined with an opioid is the limit for severe pain because the FDA has recommended that by 2014 all opioid combination drugs contain no more than 325 mg of APAP.[68] In addition, the total APAP daily dose for this recommendation remains less than 3,000 mg.

CONCLUSIONS

Combining two analgesic agents having distinct pharmacological mechanisms of action has the potential to provide profound pain relief while minimizing adverse effects. When we incorporated quantitative clinical evidence when assessing the efficacy of therapeutic doses of the ibuprofen-APAP combination, we found that this combination is more effective than are the individual agents administered alone. When we compared single and combination analgesics for pain management after third-molar extractions, the ibuprofen-APAP combination appeared to provide analgesia at least equivalent to those of commonly prescribed opioid combination formulations (Table 1[10,18,44,59,60]). In addition, there was little indication that adverse reactions are more frequent with the administration of the ibuprofen-APAP combination than with the administration of the individual components as long as maximum recommended doses of both components are not exceeded. To avoid exceed-

ing the recently revised downward maximum recommended dose of APAP (3,000 mg per day), dentists should warn patients to avoid any other products containing APAP and to follow dosing instructions.[67,68] If the combination of ibuprofen and APAP is inadequate, the addition of an opioid to the ibuprofen-APAP combination appears to be appropriate.

The demonstrated improvement in postoperative pain relief for the combination of ibuprofen and APAP provides another strategy for pain management and an alternative to prescription opioid formulations after third-molar extraction surgery. ■

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