OFIRMEV: An Old Drug Becomes New Again

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Acetaminophen is an old drug that is now available in an intravenous formulation. Its advantages and disadvantages are reviewed, including its potential role in multimodal postoperative pain therapy.

Key Words: Intravenous acetaminophen; Postoperative pain control; Multimodal analgesia.

Effective treatment of acute postoperative dental pain often requires a multimodal pain management approach—the use of multiple complementary analgesics with different mechanisms and sites of action—as a means of optimizing analgesic efficacy and reducing opioid-related adverse effects.^{1,2} The American Society of Anesthesiologists Task Force on Acute Pain Management advocates that unless contraindicated, patients should receive an around-the-clock regimen of nonopioid analgesics as first-line agents and for opioids to be used as adjunctive agents.³ The choices of medication, dose, route, and duration of therapy are determined by the practitioner and should be individualized taking into consideration the patient's medical history and physical health and the surgical procedure being performed.³

A new component in such a multimodal analgesic strategy is OFIRMEV (Cadence Pharmaceuticals, San Diego, Calif), an intravenous (IV) formulation of acetaminophen approved by the US Food and Drug Administration in 2011 for the management of mild to moderate pain, the management of moderate to severe pain with adjunctive opioid analgesics, and the reduction of fever in patients 2 years and older.⁴

Although IV acetaminophen is relatively new in the US, the same formulation has been used extensively in over 80 countries since 2002.⁵ Evidence from randomized clinical trials has found IV acetaminophen to be a

safe, effective, and well-tolerated analgesic agent in the treatment of acute postoperative pain associated with a number of surgical procedures, including third-molar extraction and orthognathic surgery.^{6,7} The goal of this paper is to examine the potential role of IV acetaminophen in dentistry.

Acetaminophen, alone or in combination with non-steroidal anti-inflammatory drugs (NSAIDs) or opioids, has been the primary and most effective analgesic therapy for the management of postoperative dental pain.^{8,9} The popularity and acceptance of acetaminophen are attributed to its relative safety and effectiveness.⁸ Acetaminophen is not associated with postoperative bleeding, gastric mucosal damage, dyspepsia, or renal injury seen with NSAIDs, nor does it cause the respiratory depression, nausea, vomiting, constipation, urinary retention, and sedation seen with opioids.^{10,11} The most important safety concern with acetaminophen is the potential for hepatotoxicity when it is used at higher than recommended doses (>4000 mg/d for adult patients)^{4,10} Compared to oral acetaminophen, IV acetaminophen reduces initial hepatic exposure by approximately twofold because of the lack of first-pass metabolism.^{7,10} Reduced hepatic exposure of IV acetaminophen thus improves its safety profile and may be of benefit to patients with compromised hepatic function.¹⁰ Nevertheless, caution must be used when administering IV acetaminophen to patients with liver dysfunction or active liver disease, alcoholism, chronic malnutrition, severe hypovolemia, or severe kidney dysfunction.⁴ IV acetaminophen is contraindicated in

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patients with severe hepatic impairment or severe active liver disease.⁴ The most common treatment-emergent adverse events associated with IV acetaminophen are nausea, vomiting, headache, and insomnia.⁴ Because of its more favorable risk/benefit profile, acetaminophen may be considered the foundation analgesic in multimodal pain management.^{9,12–14}

Dentists can administer analgesics in a variety of ways, with safety, efficacy, speed of onset, ease of administration, and cost being important factors to consider in the drug and route of administration used. Nonopioid analgesics are most often given via the oral route; however, many surgical patients are restricted from oral intake or unable to take oral medications because of sedation or postoperative nausea and vomiting.^{10,15,16} The oral route may also be less efficacious because intraoperative opioids, inhaled anesthetics, and surgical stress can delay gastric emptying, thereby reducing gastrointestinal absorption of orally administered drugs.^{17,18} Intravenous administration of acetaminophen would be an ideal route in the immediate postoperative period, especially in situations where a patient is unable to take medications by mouth or when a faster onset of analgesia is desired.^{10,11} IV acetaminophen is dispensed as a 100-mL single-use vial containing 1000 mg acetaminophen and is given over 15 minutes as an IV infusion.⁴

The primary analgesic effect of acetaminophen is thought to be due to a central nervous system site of action involving cyclooxygenase (COX) inhibition.^{5,10} Passive diffusion of acetaminophen into the central nervous system appears to be enhanced by a high plasma to cerebrospinal fluid (CSF) concentration gradient, with acetaminophen concentrations in the CSF being linearly dose proportional with plasma levels.¹⁹ IV acetaminophen has been shown to achieve higher maximum concentrations and earlier time to maximum concentration compared to bioequivalent oral doses with less intrasubject variability.^{15,16,20–22} Mean maximum concentration after a standard 15-minute infusion of 1 g acetaminophen is approximately 70% higher than the mean maximum concentration observed at equivalent oral doses.²² Peak CSF plasma concentrations of IV acetaminophen are 60% higher than with oral administration.²² Time to maximum concentration for IV acetaminophen occurs at the end of the 15-minute infusion compared to >45 minutes with oral acetaminophen.^{4,22} The earlier and higher peak plasma and CSF maximum concentrations observed with IV acetaminophen may be responsible for the more rapid onset and higher peak efficacy of IV acetaminophen compared with oral acetaminophen.²² It is important to note that the higher peak concentrations achieved by IV acetaminophen remain far below the concentration consid-

ered the threshold for potential hepatotoxicity; therefore, there is no compromise in safety when administering acetaminophen intravenously.^{11,15}

After oral surgical procedures, postoperative pain is most severe 3–5 hours following surgery and improves gradually over time.^{23,24} Rapid onset of analgesic action is critical, as studies suggest that preemptively blocking postoperative pain can limit the initiation of central pain receptor sensitization, resulting in a decrease in overall pain perception, pain duration, and need for opioid analgesics.¹³ Onset of the analgesic effect of IV acetaminophen is rapid. In a randomized, double-blinded, placebo-controlled trial comparing the onset of analgesia between equivalent doses of oral and IV acetaminophen in patients with moderate to severe pain after impacted third-molar extraction, IV acetaminophen provided a clinically significant faster onset of meaningful pain relief (8 minutes IV vs 37 minutes oral) and decreased time to achieving maximal pain relief (15 minutes IV vs 1 hour oral).¹⁵ The analgesic effect of IV acetaminophen lasts for 4–6 hours.⁴ IV acetaminophen has also been shown to be superior to oral acetaminophen in reliably obtaining therapeutic concentrations and maintaining higher plasma concentrations.²⁵ In a study comparing plasma levels achieved in the early postoperative period by equivalent doses of oral and IV acetaminophen, 96% of patients given IV acetaminophen achieved therapeutic plasma concentrations versus only 67% of patients receiving an oral dose.^{10,25}

The efficacy of IV acetaminophen in managing postoperative pain and decreasing the need for opioids has been demonstrated in a number of randomized placebo-controlled trials.^{6,7} Compared with other analgesics in the treatment of moderate to severe postoperative pain, IV acetaminophen 1 g has a comparable efficacy to ketorolac 30 mg after total hip or knee replacement, diclofenac 75 mg after orthognathic surgery or orthopedic surgery, metamizol 2.5 g after aortic aneurysm repair, and morphine 10 mg after surgical removal of impacted third molar.^{14,16,26} In patients who had undergone surgical third-molar extraction complaining of moderate to severe postoperative pain, the use of a 1 g dose of IV acetaminophen was compared with that of a 2 g dose of IV acetaminophen and with placebo.^{15,16} In this study, both active treatment groups provided more effective and longer duration of analgesia and better scores on patients' global evaluation (ie, good–excellent) compared to placebo.¹⁶ In another controlled study, acetaminophen administered intravenously as its prodrug propacetamol 2 g (equivalent to acetaminophen 1 g) was shown to have an analgesic effect indistinguishable from that of intramuscular morphine (10 mg) with better tolerability.²⁶

Postoperative nausea and vomiting is a common and unpleasant adverse effect associated with dental surgery performed under IV sedation or general anesthesia, with reported incidence rates between 20 and 30%.²⁷ Postoperative nausea and vomiting is associated with increased morbidity (ie, bleeding, hematoma, wound dehiscence, aspiration) that may prolong recovery or result in unanticipated hospital admissions.²⁷ Decreasing opioid consumption has been suggested as the most effective, safest, and least expensive way to reduce opioid-related adverse effects.^{11,27} Although systematic reviews and meta-analyses show that IV acetaminophen used in combination with patient-controlled opioid analgesia may reduce opioid requirements by 20–30%, these reductions in dose do not consistently translate into reduced incidence of opioid-related postoperative nausea and vomiting.^{6,7,10}

Until the introduction of IV acetaminophen, the only other nonopioid injectable analgesics available in the US were NSAIDs: IV ketorolac and IV ibuprofen (Caldolor, Cumberland Pharmaceuticals Inc).^{5,28} The pathogenesis of dental pain is primarily inflammation. Thus, NSAIDs have been described as being more effective analgesics in treating dental pain than acetaminophen and opioids, which lack anti-inflammatory action.^{23,29} NSAIDs produce their analgesic and anti-inflammatory effects by inhibiting COX isoenzymes COX1/COX-2 and blocking peripheral and central production of prostaglandin.^{11,29} Analgesic and anti-inflammatory effects of NSAIDs are primarily due to inhibition of COX-2, whereas the adverse effects (ie, renal dysfunction, gastrointestinal mucosal damage, platelet inhibition) are mediated by inhibition of COX-1.^{11,29} The specificity of individual NSAIDs for the COX isoenzymes differs and has significant implications in terms of analgesic potency and incidence of adverse effects.²⁹ IV ketorolac, a preferential COX-1 inhibitor, is currently the IV nonopioid analgesic of choice in the US due to its efficacy and low cost.⁵ Due to its high degree of COX-1 selectivity, IV ketorolac is only approved for use in adult patients for the short-term (5 days or fewer) management of moderate to severe pain requiring analgesia at the opioid level; its use prior to major surgery and intraoperatively is contraindicated.⁵ IV ibuprofen is indicated for use only in adults for the management of mild to moderate pain, management of moderate to severe pain as an adjunct to opioid analgesics, and reduction of fever.^{28,29} IV ibuprofen has a safer clinical profile than ketorolac due to its more balanced affinity for COX-1/COX-2 and is approved for preoperative administration with no limitations on its duration of use.^{28,29} Nevertheless, all NSAIDs carry risks of serious gastrointestinal, cardiovascular, renal, and bleeding adverse effects.⁵ In situations where IV NSAIDs are not

approved (ie, pediatric patients) or not clinically appropriate (ie, patients with history of peptic ulcer disease, renal disease, or surgeries with a high risk of postoperative bleeding), IV acetaminophen can serve as a viable alternative when an IV route of administration is needed.^{10,28,29}

For many outpatient dental procedures performed under general anesthesia or IV sedation, IV acetaminophen administered in the immediate postoperative period may provide sufficient analgesia to address mild to moderate pain, obviating the need for or decreasing NSAID and opioid dosing and their associated side effects.^{5,10,11} The primary advantage of IV acetaminophen is as a means to provide nonopioid analgesia in patients with mild to moderate pain in whom the oral route is not possible and IV NSAIDs are contraindicated. IV acetaminophen provides a method of achieving rapid therapeutic concentrations that can subsequently be maintained by oral acetaminophen.^{30,31} In conclusion, IV acetaminophen is a new IV nonopioid analgesic, which may find a role in dentistry for the management of postoperative pain.

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REFERENCES

1. Crews JC. Multimodal pain management strategies for office-based and ambulatory procedures. *JAMA*. 2002;288:629–632.
2. Myles PS, Power I. Clinical update: postoperative analgesia. *Lancet*. 2007;369:810–812.
3. American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology*. 2012;111:248–273.
4. Cadence Pharmaceuticals Inc. OFIRMEV (acetaminophen) injection [prescribing information]. San Diego, CA: Cadence Pharmaceuticals Inc; 2010.
5. Smith HS. Perioperative intravenous acetaminophen and NSAIDs. *Pain Med*. 2011;12:961–981.
6. Macario A, Royal MA. A literature review of randomized clinical trials of intravenous acetaminophen (paracetamol) for acute postoperative pain. *Pain Pract*. 2011;11:290–296.
7. McNicol ED, Tzortzopoulou A, Cepeda MS, Fracia MB, Farhat T, Schumann R. Single-dose intravenous paracetamol or propacetamol for prevention or treatment of postoperative pain: a systematic review and meta-analysis. *Br J Anaesth*. 2011;106:292–297.

8. Guggenheimer J, Moore PA. The therapeutic applications of and risks associated with acetaminophen use: a review and update. *J Am Dent Assoc.* 2011;142:38–44.
9. Haas DA. An update on analgesics for the management of acute postoperative dental pain. *J Can Dent Assoc.* 2002;68:476–482.
10. Jahr JS, Lee VK. Intravenous acetaminophen. *Anesthesiol Clin.* 2010;28:619–645.
11. Pasero C, Stannard D. Role of IV acetaminophen in acute pain management: a case-illustrated review. *Pain Manag Nurs.* 2012;13:107–124.
12. Duggan ST, Scott LJ. Intravenous paracetamol (acetaminophen). *Drugs.* 2009;69:101–113.
13. Fletcher MC, Spera JF. Management of acute postoperative pain after oral surgery. *Dent Clin N Am.* 2012;56:95–111.
14. Gorocs TS, Lambert M, Rinne T. Efficacy and tolerability of ready-to-use intravenous paracetamol solution as monotherapy or as an adjunct analgesic therapy for postoperative pain in patients undergoing elective ambulatory surgery: open, prospective study. *Int J Clin Pract.* 2009;63:112–120.
15. Moller LP, Sindet-Pedersen S, Petersen CT, Juhl GI, Dillenschneider A, Skoglund LA. Onset of acetaminophen analgesia: comparison of oral and intravenous routes after third molar surgery. *Br J Anaesth.* 2004;94:642–648.
16. Moller LP, Juhl GI, Payen-Champenois C, Skoglund LA. Intravenous acetaminophen (paracetamol): comparable analgesic efficacy, but better local safety than its prodrug, propacetamol, for postoperative pain after third molar surgery. *Anesth Analg.* 2005;101:90–96.
17. Joshi GP, Ogunnaike BO. Consequences of inadequate postoperative pain relief and chronic persistent postoperative pain. *Anesthesiol Clin North America.* 2005;23:21–36.
18. Juhl GI, Norholt SE, Tonnesen E, Hiesse-Provost O, Jensen T. Analgesic efficacy and safety of intravenous paracetamol (acetaminophen) administered as a 2 g starting dose following third molar surgery. *Eur J Pain.* 2006;10:371–377.
19. Jensen LL, Handberg G, Brosen K, Schmedes A, Ording H. Paracetamol concentrations in plasma and cerebrospinal fluid. *Eur J Anesthesiol.* 2004;21:193.
20. Holmer Pettersson P, Owall A, Jakobsson J. Early bioavailability of paracetamol after oral and intravenous administration. *Acta Anesthesiol Scand.* 2004;48:867–870.
21. Jarde O, Boccard E. Parenteral versus oral route increases paracetamol efficiency. *Clin Drug Invest.* 1997;14:474–481.
22. Singla NK, Parulan C, Samson R, et al. Plasma and cerebrospinal fluid pharmacokinetic parameters after single-dose administration of intravenous, oral or rectal acetaminophen. *Pain Pract.* 2012;12:523–532.
23. Ong KS, Seymour RA. Pathogenesis of post-operative oral surgical pain. *Anesth Prog.* 2003;50:5–17.
24. Seymour RA, Meechan JG, Blair GS. An investigation into postoperative pain after third molar surgery under local anesthesia. *Br J Oral Maxillofac Surg.* 1985;23:410.
25. Van der Westhuizen J, Kuo PY, Reed PW, Holder K. Randomised controlled trial comparing oral and intravenous paracetamol (acetaminophen) plasma levels when given as preoperative analgesia. *Anaesth Intensive Care.* 2011;39:242–246.
26. Van Aken H, Thys L, Veekman L, Buerkle H. Assessing analgesia in single and repeated administrations of propacetamol for post operative dental pain: comparison with morphine after dental surgery. *Anesth Analg.* 2004;98:159–165.
27. Cruthirds D, Sims PJ, Louis PJ. Review and recommendations for the prevention, management, and treatment of postoperative and postdischarge nausea and vomiting. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2013;115:601–611.
28. Cumberland Pharmaceuticals Inc. Caldolor (ibuprofen) injection, for intravenous use [product information]. Nashville, TN: Cumberland Pharmaceuticals Inc; 2009.
29. Ong KS, Seymour RA. An evidence-based update on the use of analgesics in dentistry. *Periodontol 2000.* 2008;46:143–164.
30. Oscier CD, Milner QJW. Peri-operative use of paracetamol. *Anaesthesia.* 2009;64:65–72.
31. Pergolizzi JV, Raffa RB, Tallarida R, Taylor R, Labhsetwar SA. Continuous multimechanistic postoperative analgesia: a rational for transitioning from intravenous acetaminophen and opioids to oral formulations. *Pain Pract.* 2011;12:159–173.