Acetaminophen Injection (OFIRMEV)

National Drug Monograph Update
March 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Indication(s) Under Review in this Document	FDA-approved Indication(s): • Management of mild to moderate pain • Management of moderate to severe pain with adjunctive opioid analgesics • Reduction of fever Off-label Use(s): Renal colic pain in emergency department setting
Dosage Form(s) Under Review	Dosage Form(s), Strength(s) • Injection for intravenous infusion. • Each 100 mL glass vial contains 1000 mg acetaminophen (10 mg/mL).

Executive Summary	
Efficacy	• Acetaminophen injection may potentially substitute for opioid analgesia for certain surgical procedures and in patients with renal colic pain; further studies are needed. • Acetaminophen injection may reduce rescue opioid requirements; however, the magnitude of rescue opioid dose reduction varies and may depend on the level of pain associated with the particular type of surgery and concurrent perioperative analgesic and anesthetic treatments.
Safety	• Acetaminophen injection seems to reduce postoperative nausea and vomiting; however, improvement in these adverse effects may be related to pain control rather than reduction in opioid use. • Whether acetaminophen injection reduces opioid harms by reducing rescue opioid use is unclear, and other surgical and treatment-related factors may influence results.
Other Considerations	• For health care staff, the fixed dosing regimen of acetaminophen injection may be more convenient than titrating opioid doses.
Potential Impact	• There is insufficient evidence at this time to support modifying the current formulary status and restrictions for acetaminophen injection.

Background

Purpose for review

To update the evidence base to evaluate whether the potential clinical impact of acetaminophen for intravenous injection warrants modification of formulary status or restrictions. This agent is currently on formulary, restricted to post-operative use and postanesthesia care units.

Issues to be determined:

- Does acetaminophen injection offer advantages over currently available alternative nonopioid analgesics used for perioperative pain management or other off-label uses?
- What is the relative impact of acetaminophen injection on patient symptoms, health care utilization and costs as they relate to potential reduction in opioid harm?

Other therapeutic options

Nonformulary Alternatives FDA-approved after 2012	Indications for Use in Adults (All agents were studied for postoperative pain)
Diclofenac sodium, intravenous bolus injection (DYLOJECT)	• management of mild to moderate pain • management of moderate to severe pain alone or in combination with opioid analgesics
Ibuprofen injection, intravenous infusion (CALDOLOR)	• management of mild to moderate pain • management of moderate to severe pain alone or in combination with opioid analgesics • reduction of fever
Ketorolac tromethamine nasal spray (SPRIX)	• short term (up to 5 days) management of moderate to moderately severe pain that requires analgesia at the opioid level

Potential Impact

Literature Search Summary

A literature search was performed on PubMed/Medline (2011 to March 2015) using the search terms intravenous, acetaminophen and OFIRMEV. The search was limited to studies performed in humans and published in the English language. Reference lists of articles were searched for relevant clinical trials.

Table 1 Impact of Acetaminophen Injection for Perioperative Pain Management

IMPACT	RESULTS	COMMENTS	REFERENCE
Acetaminophen i.v Versus Morphine 10 mg i.v., Acute Pain from Isolated Limb Trauma, Emergency Department			
No reduction in patients requiring rescue analgesia use	Required MOR i.v.: 29.6% vs. 28.6% (NSD)	Age criteria were limited to > 15 and < 66 years to minimize risks of morphine. Treatments were similar in pain reduction. AEs were recorded if SBP < 90 mm Hg; respiratory rate < 10; Glasgow Coma Scale < 13; O_2 saturation < 95%; anaphylaxis (counts per AE not specified).	*Craig (2012)*[1]
Reduced incidence of AEs	7.4% vs. 28.6% (p = .03)		
Acetaminophen i.v. Versus Meperidine i.v., Intrapartum Analgesia			
Reduced incidence of AEs	AEs: 0% vs. 64%	Treatments were similar in pain reduction. Potential MEP substitute	**Elbohoty (2012)**[2]
Acetaminophen i.v. Versus Placebo, Abdominal Laparoscopic Surgery			
No reduction in patients requiring rescue medication use	56.5% vs. 64.3% (NSD)		*Wininger (2010)*[3]
No reduction in rescue opioid use	MOR Equivalents, mean (mg): T0 to T12, 18.3 vs. 16.1 mg; T12 to T24, 19.4 vs. 19.0 (NSD)		
Increased incidence of certain	Incision site pain: 5.5% vs. 0% (p = .018)	None of the incision site pain or dyspnea events were	

IMPACT	RESULTS	COMMENTS	REFERENCE
AEs	Dyspnea: 7.0% vs. 0% (p = .021)	deemed to be related to APAP.	
Acetaminophen i.v. Versus Placebo, Total Abdominal Hysterectomy			
Reduced hospital stay	I.v. APAP vs. PBO: 5 vs. 6 d (Δ 1 d) (p < .05)		*Arici (2009)*[4]
Reduced rescue opioid use	MOR use via PCA: 25.9 vs. 35.7 vs. 62.9 mg for Preemptive APAP vs. Intraop APAP vs. PBO Δ MOR, pre-op APAP vs. PBO = 37 mg PCA		
No reduction in respiratory depression	NSD in SpO2 < 95% No cases of respiratory depression requiring naloxone		
No reduction in incidence of sedation	Sedation: NSD		
No reduction in treatment for PONV	NSD in rescue antiemetic use	Pre-op i.v. APAP	**Moon (2011)**[5]
Reduced rescue opioid use	HM PCA use: 2.9 vs. 4.2 mg; Δ HM = 1.3 mg (8.7 mg MOR i.v.)		
No reduction in rescue NSAID use	NSD in ketorolac use		
Reduced incidence of sedation	Sedation: 11% vs. 29%		
Acetaminophen i.v. Versus Placebo, Various Surgeries			
No reduction in Time to Extubation, after elective CABG	NSD in TTE		*Petterson (2006)*[6]
Reduced Rescue Opioid Use, after tonsillectomy	MEP use: 18 vs. 82 mg i.v.; Δ MEP = 64 mg (6.4 mg MOR i.v.)	Tonsillectomy is a less painful procedure.	*Atef and Fawaz (2008)*[7]
Reduced Rescue Opioid Use, after total hip / knee replacement	MOR use: 38.3 vs. 57.4 mg; Δ MOR = 19.1 mg i.v.		*Sinatra (2005)*[8]
Systematic Review of Acetaminophen i.v. vs. Placebo RCTs, Various Surgeries			
Reduced (pain-associated) PONV	**RR** (95% CI): 0.73 (0.60–0.88) for nausea 0.63 (0.45–0.88) for vomiting **NNT:** 12.3 (7.6–32.3) for nausea 14.2 (8.3–50.8) for vomiting	Timing of treatment is important for benefit. Seen with pre-op and intra-op but not postop IV APAP. Reduction in PONV was associated with reduction in pain (avg 0.9 on 11-pt NRS) rather than reduction in opioid use (9 mg morphine equivalents)	**Apfel (2013)**[9]
Reduced rescue analgesia use	**OR (95% CI):** 0.12 (0.13, 0.33)		*McNicol (2011)*
Reduced opioid use	Δ **MOR i.v., mg:** 4 h, -1.3 (-1.7, -0.9) 6 h, -2.0 (-2.6, -1.6)		
Meperidine-Acetaminophen i.v. vs. Meperidine-Placebo, Major Abdominal or Pelvic Surgery, in ICU			
No reduction in ICU Stay	Similar ICU LOS	No report of reduced pneumonia No pts had respiratory depression or required reintubation	*Memis (2010)*[10]
Reduced Time to Extubation	Reduced TTE (Δ 2.3 h)		
Reduced use of treatment for PONV	1/20 [5%] vs. 7/20 [35%] (p < .05)		
Reduced incidence of PONV	PONV incidence: 1/20 (5%) vs. 8/20 (40%); p < .05		
Reduced Opioid Use	MEP use (76.75 ± 18.2 mg vs. 198 ± 66.4		

IMPACT	RESULTS	COMMENTS	REFERENCE
	mg) (*P* < .01); Δ MEP dose (121 mg; ~ 12.1 mg MOR i.v.)		
Reduced intensity of sedation	Sedation scores: 1.83 ± 0.5 vs. 2.3 ± 0.8		
Low-dose Tramadol-Acetaminophen i.v. vs.Tramadol Patient-controlled Analgesia, Spinal vertebral surgery			
Reduced use of treatment for PONV	Metoclopramide use: 1.3 vs. 5.7 mg (p < .001)		**Emir (2010)**[11]
Reduced Opioid Use	**I.m. MEP use**: 20.8 vs. 45.4 mg (p=0.006); Δ MEP use, 24.6 mg i.m. (2.5 mg MOR i.v.) **Tramadol**: 153 vs. 276 mg (p < .001) NSD in remifentanil use intra-op.		
No reduction in respiratory depression and cardiovascular AEs	NSD in respiratory depression, bradycardia or hypotension		
Reduced intensity of nausea and incidence of vomiting	Nausea scores: max. Δ = 0.4 points on 4-pt scale (p<0.05). Vomiting: 4/30 (13%) vs. 17/30 (57%; p = .02)		
No reduction in incidence of sedation	Sedation: NSD		
Increased Drug Costs	€12.6 vs. €4.5 (p < .001).		
Acetaminophen i.v. vs. Ibuprofen p.o., C-section			
No reduction in rescue opioid use	MOR use: NSD	Study treatments and spinal anesthesia were given pre-op. Morphine i.v. PCA was started post-op.	*Alhashemi (2006)*[12]
Numerically increased postop nausea / vomiting	Nausea: 18.2% vs. 8.7% (NSD) Vomiting: 18.3% vs. 0% (p = .05)		
Decreased pruritus	10/22 vs. 19/23 (p = .013)		

All doses of acetaminophen i.v. are 1 g (single dose or every 6 hours) unless specified otherwise.

AE, Adverse event; Aldrete Score (Activity, Respiration, Circulation, Consciousness, Color); APAP, Acetaminophen; HM, Hydromorphone; MEP, Meperidine; MOR, Morphine; NSD, No statistically significant difference; PBO, Placebo; PONV, Postoperative nausea/vomiting. Δ, Absolute difference.

Italicized Author / Year indicates reference was included in the 2012 abbreviated drug monograph for intravenous acetaminophen

Table 2 Impact of Acetaminophen Injection for Nonsurgical Pain Management

IMPACT	RESULTS	COMMENTS	REFERENCE
Acetaminophen i.v. vs. Morphine 0.1 mg/kg i.v., Renal colic in ED			
No reduction in incidence of AEs	AEs: Δ 9%, 95% CI -7% to 26%; NSD	Potential opioid substitute?	**Serinken (2012)**[13]
No reduction in incidence of AEs	AEs: Δ –8%, NSD	Potential opioid substitute?	*Bektas (2009)*[14]
No reduction in patients (%) requiring rescue opioid	Δ: –3%		

Risk Evaluation

As of 6 March 2015

Sentinel event advisories	• None

Projected Place in Therapy

- Based on the review of the available moderate-quality evidence, pre-operative acetaminophen injection is likely to have a beneficial impact on reducing patient symptoms such as postoperative nausea and vomiting, which may be related to reduction in pain intensity rather than reduction in opioid use.
- Acetaminophen injection has an uncertain impact on reducing opioid harms such as sedation and respiratory depression or time to extubation despite fairly consistent study results showing reduced opioid requirements; and it has an uncertain impact on health care utilization such as length of hospital or intensive care unit stay in patients with postoperative pain following different types of surgery.
- The impact of i.v. acetaminophen on patient symptoms and health care utilization may vary by type of surgical procedure and the types and quantities of concomitant perioperative medications such as benzodiazepines and other anesthetic agents.
- No pharmacoeconomic studies relevant to VA were found.
- Additional well-designed studies are needed to determine the relative clinical benefit-harm-cost value of acetaminophen injection for postoperative pain and nonsurgical acute pain.
- The VA/DoD clinical practice guideline for management of postoperative pain is being updated and will likely recommend perioperative use of intravenous acetaminophen.

Prepared March 2015
Contact person: Francine Goodman, National PBM Clinical Pharmacy Program Manager – Formulary, Pharmacy Benefits Management Services (10P4P)

References

[1] Craig M., Jeavons R., Probert J., Benger J. Randomised comparison of intravenous paracetamol and intravenous morphine for acute traumatic limb pain in the emergency department. Emerg Med J 2012;29:37-39

[2] Elbohoty AE, Abd-Elrazek H, Abd-El-Gawad M, Salama F, El-Shorbagy M, Abd-El-Maeboud KH. Int J Gynaecol Obstet. 2012 Jul;118(1):7-10 [Egypt]

[3] Wininger S., Miller H., Minkowitz H., et al. A randomized, double-blind, placebo-controlled, multicenter, repeat-dose study of two intravenous acetaminophen dosing regimens for the treatment of pain after abdominal laparoscopic surgery. Clinical Therapeutics 2010; 32(14):2348-69

[4] Arici S, Gurbet A, Türker G, Yavaşcaoğlu B, Sahin S. Preemptive analgesic effects of intravenous paracetamol in total abdominal hysterectomy. Agri. 2009 Apr;21(2):54-61

[5] Moon YE, Lee YK, Lee J, Moon DE. The effects of preoperative intravenous acetaminophen in patients undergoing hysterectomy. *Arch Gynecol Obstet*. 2011;284(6):1455-1460

[6] Pettersson P., Jakobsson J., Owal A. Plasma concentrations following repeated rectal or intravenous administration of paracetamol after heart surgery. Acta Anaesthesiol Scand 2006; 50: 673–677

[7] Atef A, Fawaz AA. Intravenous paracetamol is highly effective in pain treatment after tonsillectomy in adults. Eur Arch Otorhinolaryngol. 2008 Mar;265(3):351-5. Epub 2007 Sep 22

[8] Sinatra R., Jahr J., Reynolds L., Viscusi E., Groudine S., Payen-Champernois C. Efficacy and safety of single and repeated administration of 1 gram intravenous acetaminophen injection (paracetamol) for pain management after major orthopedic surgery. Anesthesiology 2005; 102(4):822-831

[9] Apfel CC, Turan A, Souza K, Pergolizzi J, Hornuss C. Intravenous acetaminophen reduces postoperative nausea and vomiting: a systematic review and meta-analysis. Pain. 2013 May;154(5):677-89

[10] Memis D, Inal MT, Kavalci G, Sezer A, Sut N. Intravenous paracetamol reduced the use of opioids, extubation time, and opioid-related adverse effects after major surgery in intensive care unit. J Crit Care. 2010 Sep;25(3):458-62 [Turkey]

[11] Emir E, Serin S, Erbay RH, Sungurtekin H, Tomatir E. Tramadol versus low dose tramadol-paracetamol for patient controlled analgesia during spinal vertebral surgery. Kaohsiung J Med Sci. 2010; 26(6):308-315 [Turkey]

[12] Alhashemi JA., Alotaibi QA., Mashaat MS., Kaid TM., Mujallid RH., Kaki AM. Intravenous acetaminophen vs oral ibuprofen in combination with morphine PCIA after cesarean delivery. Can J Anesth 2006;53:1200-1206

[13] Serinken M, Eken C, Turkcuer I, Elicabuk H, Uyanik E, Schultz CH. Intravenous paracetamol versus morphine for renal colic in the emergency department: a randomised double-blind controlled trial. Emerg Med J. 2012 Nov;29(11):902-5

[14] Bektas F., Eken C., Karadeniz O., Goksu E., Cubuk M., Cete Y. Intravenous paracetamol or morphine for the treatment of renal colic: a randomized, placebo-controlled trial. Ann Emerg Med 2009;54:568-574