Acetaminophen: Foundation of Multi-modal Analgesia

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PANA
Hershey
Disclosures

- Art Zwerling, is a paid consultant to Cadence Inc.
- Art Zwerling, is a member of the Cadence Inc. speaker’s bureau.
- Art Zwerling, is a member of the Hospira speaker’s bureau.
- There will be no discussion of off label utilization of Ofirmev® during this presentation.
Objectives

• Participants will review the pharmacokinetics and pharmacodynamics of intravenously administered acetaminophen.
• Attendees will compare and contrast various therapeutic options for multi-modal analgesia
• Learners will review the physiology of acute nociceptive and inflammatory pain processes.
• Participants will review various strategies for opioid sparing anesthetic management for high risk patients
OFIRMEV™
(acetaminophen) injection

A Non-Opioid, Non-NSAID Analgesic for Perioperative Pain Management

Please see Full Prescribing Information for OFIRMEV
Dear God, when will this presentation end?

DEATH BY POWERPOINT
Perioperative Analgesia: What Do We Still Know?

Paul F. White, PhD, MD, Henrik Kehlet, MD, PhD & Spencer Liu, MD

Anesth Analg 2009; 108:1364-1367
<table>
<thead>
<tr>
<th>No.</th>
<th>Author(s)</th>
<th>Title</th>
<th>Journal and Year</th>
<th>Page Numbers</th>
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</thead>
<tbody>
<tr>
<td>1.</td>
<td>Reuben SS, Connelly NR</td>
<td>Postoperative analgesic effects of celecoxib or rofecoxib after spinal fusion surgery</td>
<td>Anesth Analg 2008;91:1221-5</td>
<td></td>
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<tr>
<td>9.</td>
<td>Reuben SS, Steinberg RB, Maciolek H, Manikantan P</td>
<td>An evaluation of the analgesic efficacy of intravenous regional anesthesia with lidocaine and ketorolac using a forearm versus upper arm tourniquet</td>
<td>Anesthesiology 2002;95:457-60</td>
<td></td>
</tr>
<tr>
<td>17.</td>
<td>Reuben SS, Buvanendran A, Kroin JS, Steinberg RB</td>
<td>Postoperative modulation of central nervous system prostaglandin E2 by cyclooxygenase inhibitors after vascular surgery</td>
<td>Anesthesiology 2006;104:411-16</td>
<td></td>
</tr>
</tbody>
</table>
Postoperative and Acute Pain

Postoperative pain
- In 2006, 46 million inpatient surgical procedures and 34.7 million ambulatory surgeries were performed in the United States\textsuperscript{1,2}
- In a national survey sampling 129 inpatients who recently underwent a surgical procedure, 73\% reported pain before discharge\textsuperscript{3}
  - Of these, 88\% reported moderate, severe, or extreme pain

Acute pain
- In 2004, approximately 61 million patients reported pain during an emergency department visit\textsuperscript{4}

Acute nociceptive & inflammatory pain

• Treat the pain as soon as possible
  (before activation of pain amplification mechanisms)

• Treat the pain as completely as possible
  at the periphery
  at the spinal level
  at the supra-spinal level
Moderate to Severe Pain Following Surgery Is Very Common

Inpatients Who Reported Pain After Surgery, Before Discharge, 2003

% Adult Inpatients Surveyed

Overall Pain After Surgery

- Slight: 12%
- Moderate: 40%
- Severe: 23%
- Extreme: 25%

n=94

Goals of Perioperative Pain Management

- Improved clinical outcomes\(^1-3\)
  - Effective pain relief
  - Better patient satisfaction

- Routine multimodal pain management\(^1,3,4\)
  - Use of non-opioid analgesics alone in mild to moderate pain, or with opioids in moderate to severe pain
  - Postoperative pain management begins prior to surgery
  - Multimodal analgesia may decrease opioid dose requirements

- The goals of the ASA guidelines include\(^5\)
  - Facilitate safe and effective acute pain management in the perioperative setting
  - Maintain patient’s functional abilities

ASA=American Society of Anesthesiologists.

Just a few words about opioids

“No Patient Shall Be Harmed By Opioid-Induced Respiratory Depression”
Proceedings of: “Essential Monitoring Strategies to Detect Clinically Significant Drug-Induced Respiratory Depression in the Postoperative Period”
Opioid Reduction

- Respiratory depression
- Ileus
- Delirium
- Immunosuppression
- Nausea & vomiting
- Pruritus
- Opioid induced hyperalgesia
Multimodal Techniques for Perioperative Pain Management

- Multimodal: Two or more analgesic agents or techniques that act by different mechanisms, providing superior analgesic efficacy

- ASA Task Force: Opioid dose-sparing effect can be achieved via addition of NSAIDs, COX-2 inhibitors, or acetaminophen

- ASA Task Force Recommendation: Unless contraindicated, all patients should receive an around-the-clock regimen of NSAIDs, COX-2 inhibitors, or acetaminophen

COX-2=cyclooxygenase-2; NSAID=nonsteroidal anti-inflammatory drug.

Multimodal Approach to Analgesia\textsuperscript{1,2}

NMDA=N-methyl-D-aspartate.

A Common Approach to Acute Pain Management

Severe Pain

Moderate Pain

Mild Pain

Opioids

Multimodal Approach to Acute Pain Management\textsuperscript{1-3}

**Severe Pain**
- **STEP 3**
  - STEPS 1&2
  - AND
  - Local anesthetic blockade
  - AND
  - Use of sustained-release opioid analgesics

**Moderate Pain**
- **STEP 2**
  - STEP 1
  - AND
  - Intermittent doses of opioid analgesics

**Mild Pain**
- **STEP 1**
  - Acetaminophen, NSAIDs, or COX-2 selective inhibitors
  - AND
  - Local anesthetic infiltration

Applied Clinical Research: 3
Groups Morone Saxatilis
Rectal Aceta  Oral Aceta  IV Aceta
Acetaminophen Overview
“Power corrupts, PowerPoint corrupts absolutely”

Edward Tufte, PhD
Plasma and Cerebrospinal Fluid Pharmacokinetic Parameters After Single-Dose Administration of Intravenous, Oral, or Rectal Acetaminophen

Plasma and Cerebrospinal Fluid Pharmacokinetic Parameters After Single-Dose Administration of Intravenous, Oral, or Rectal Acetaminophen
Plasma and Cerebrospinal Fluid Pharmacokinetic Parameters After Single-Dose Administration of Intravenous, Oral, or Rectal Acetaminophen
Conclusions: These results demonstrate that earlier and greater CSF penetration occurs as a result of the earlier and higher plasma peak with IV administration compared with PO or PR.
Indication for OFIRMEV™ (acetaminophen) injection

- OFIRMEV (acetaminophen) injection is indicated for:
  - Management of mild to moderate pain
  - Management of moderate to severe pain with adjunctive opioid analgesics
  - Reduction of fever
Important Safety Information for OFIRMEV™ (acetaminophen) injection

- OFIRMEV should be administered only as a 15-minute infusion.
- Do not exceed the maximum recommended daily dose of acetaminophen. Administration of acetaminophen by any route in doses higher than recommended may result in hepatic injury, including the risk of severe hepatotoxicity and death.
- OFIRMEV is contraindicated in patients with severe hepatic impairment, severe active liver disease or with known hypersensitivity to acetaminophen or to any of the excipients in the formulation. Acetaminophen should be used with caution in patients with the following conditions: hepatic impairment or active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia, or severe renal impairment.
- Discontinue OFIRMEV immediately if symptoms associated with allergy or hypersensitivity occur. Do not use in patients with acetaminophen allergy.
- The most common adverse reactions in patients treated with OFIRMEV were nausea, vomiting, headache, and insomnia in adult patients and nausea, vomiting, constipation, pruritus, agitation, and atelectasis in pediatric patients.
- The antipyretic effects of OFIRMEV may mask fever in patients treated for post-surgical pain.
- For additional product information, please see full Prescribing Information.
Acetaminophen

- Acetaminophen=paracetamol=N-acetyl-p-aminophenol (APAP)
- Acetaminophen is a non-opioid, non-NSAID
- Acetaminophen is frequently prescribed in multimodal analgesic regimens¹
  - A component in oral combinations (such as Vicodin®, Lortab®, and Percocet®)²-⁴
- Well-established safety profile⁵
  - Hepatotoxicity is rare when used at therapeutic doses⁶-⁷
- OFIRMEV™ is the first IV formulation of acetaminophen available in the United States⁸
  - More than 400 million doses of IV acetaminophen have been distributed in over 60 countries worldwide⁶

Administration of acetaminophen by any route in doses higher than recommended may result in hepatic injury, including the risk of severe hepatotoxicity and death⁸

Vicodin is a registered trademark of Abbot Inc., Lortab is a registered trademark of UCB Inc., and Percocet is a registered trademark of Endo Inc.

Pharmacokinetics of IV Acetaminophen vs Oral Acetaminophen

PK study comparing IV to oral acetaminophen*

- Mean acetaminophen concentration over time: 6-hour dosing regimen (arrows) of IV or oral acetaminophen in healthy adults.
- Mean maximum concentration ($C_{max}$) is up to 70% higher in IV than in oral acetaminophen.
- Overall exposures (area under the concentration-time curve [AUC]) are very similar for IV and oral acetaminophen.
- IV acetaminophen accumulation is similar to that of oral acetaminophen.

Graph showing Acetaminophen Plasma Concentration (µg/mL) vs Time (h)

*Of the 38 randomly assigned patients, 34 patients who received IV acetaminophen 1g and 33 patients who received oral acetaminophen 1g had plasma concentrations measured.

1. Rapid release liquid oral acetaminophen

Pharmacodynamics of OFIRMEV™ (acetaminophen) Injection

- Onset of action: within 15 minutes of administration for both pain and fever\(^1,2\)
- Peak effect: within an hour of administration\(^1,2\)
- Duration of effect: 4 to 6 hours\(^1,2\)
- Repeated doses of 1000 mg every 6 hours for 48 hours have not been shown to cause a significant effect on platelet aggregation\(^3\)

Metabolism of OFIRMEV™ (acetaminophen) injection

- IV acetaminophen bypasses first-pass liver metabolism\(^1\)

- Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves 3 principal separate pathways\(^2\):
  - Glucuronidation
  - Sulfation
  - Oxidation

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Cannabinoid Receptor Hypothesis

AM404: Acetaminophen Metabolite

Anandamide: Endogenous Cannabinoid
Clinical Studies for OFIRMEV™ (acetaminophen) injection
Clinical Study in Orthopedic Surgery
(Sinatra et al)

- Randomized, double-blind, placebo-controlled multidose study in total hip or knee arthroplasty
- 7 US centers, N=151 patients (n=101; not including propacetamol patients)
- Moderate to severe pain; patients randomly assigned to 1 of 3 treatment groups
  - 1 g OFIRMEV™ (acetaminophen) injection
  - 2 g propacetamol IV*
  - Placebo
- Rescue medication: PCA morphine plus PRN bolus doses available
- Treatment was initiated morning following surgery
- Endpoints: pain intensity, pain relief, patient satisfaction and morphine use were measured at selected intervals

*Please note: propacetamol is not available for commercial use in the United States.

PCA=patient-controlled analgesia; PRN=as needed.

Clinical Study in Orthopedic Surgery: Results (Sinatra et al)

<table>
<thead>
<tr>
<th></th>
<th>IV Acetaminophen</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient satisfaction: good to excellent at 24 h</td>
<td>40.8%</td>
<td>23.1%</td>
<td>0.004†,‡</td>
</tr>
<tr>
<td>Median time to first use of rescue</td>
<td>3.0 h</td>
<td>0.8 h</td>
<td>0.0001</td>
</tr>
<tr>
<td>Morphine consumption over 24 h†</td>
<td>38.3 mg (33%↓)</td>
<td>57.4 mg</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Safety (adverse reactions)</td>
<td>IV acetaminophen is comparable to placebo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† Based on Cochran-Mantel Haenszel Test
‡ Clinical benefit of reduced opioid consumption was not demonstrated

Clinical Study in Abdominal Laparoscopic Surgery

- A phase 3, multicenter, randomized, double-blind, placebo-controlled, 24-hour study of the efficacy and safety of IV acetaminophen in abdominal laparoscopic surgery
- IV or oral rescue medication was available to all patients
- N=244 subjects; 17 sites in the United States
- Treatment was initiated morning following surgery
- Primary Endpoint
  - Assess the efficacy over the course of 24 hours of repeated doses (q6h) of acetaminophen injection 1000 mg vs placebo in the treatment of patients with postoperative pain who underwent abdominal laparoscopic surgery

Clinical Study in Abdominal Laparoscopic Surgery: Results

Most common surgical procedures included hysterectomy, cholecystectomy, and hernia repair.

Mean SPID24 (VAS 100 mm)

-45.2

-194.1

P=0.0068

SPID24=Sum of pain intensity differences, based on VAS score, from baseline at 0 to 24 h
VAS=Visual analogue scale

### Reduced Opioid Consumption Across a Variety of Surgeries*

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Study Design</th>
<th>Primary Endpoint</th>
<th>Reduction in Opioid Consumption*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total hip replacement at 24 h</td>
<td>Randomized, placebo-controlled study with subjects randomized to receive placebo or OFIRMEV 1 g + PCA morphine.</td>
<td>Pain intensity difference (4-point categorical scale) at 24 h postdose</td>
<td>57.4 mg (n=52) vs 38.3 mg (n=49)</td>
</tr>
<tr>
<td>Abdominal or pelvic at 24 h</td>
<td>Randomized, placebo-controlled study with subjects randomized to receive placebo or OFIRMEV 1 g + PCA morphine.</td>
<td>Pain intensity difference (4-point categorical scale) at 24 h postdose</td>
<td>(P&lt;0.016) vs (P&lt;0.001)</td>
</tr>
<tr>
<td>Major abdominal or pelvic at 24 h</td>
<td>Randomized, placebo-controlled study with subjects randomized to receive placebo or OFIRMEV 1 g + PCA morphine.</td>
<td>Pain intensity difference (4-point categorical scale) at 24 h postdose</td>
<td>82 doses (n=38) vs 18 doses (n=38)</td>
</tr>
<tr>
<td>Adult tonsillectomy at 0-24 h</td>
<td>Randomized, prospective, placebo-controlled double-blind trial with 2 parallel groups.</td>
<td>Patient need for rescue analgesic during the first 24 h after surgery.</td>
<td>(P&lt;0.001)</td>
</tr>
</tbody>
</table>

ICU, intensive care unit; IM, intramuscular; Q6h, every 6 hours.

*Clinical benefit of reduced opioid consumption was not demonstrated; †Study was prematurely terminated because of visible particulates in placebo vials. Planned enrollment was 140 subjects.

## Improved Patient Satisfaction Across a Variety of Surgeries

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Study Design</th>
<th>Primary Endpoint</th>
<th>% of Patients Reporting Good or Excellent Satisfaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal laparoscopy</td>
<td>Randomized, double-blind, placebo-controlled, multicenter, parallel-group study</td>
<td>Pain relief measured on a 5-point verbal scale over 6 h with a weighted sum of pain intensity score differences from 0 to 24 h, comparing OFIRMEV 1 g with combined placebo group.</td>
<td>70.3% (n=108) 86.9% (n=92) (P=0.0004)$^\dagger\ddagger$</td>
</tr>
<tr>
<td>Hip/knee replacement</td>
<td>Randomized, double-blind, placebo-controlled, single- and repeated-dose study</td>
<td>Pain intensity score and subject global evaluation of efficacy at bedtime with repeated doses.</td>
<td>70.3% 86.9% (n=52) 85.7% 92.7% (n=49) (P=0.0018)$^\dagger\ddagger$</td>
</tr>
</tbody>
</table>

*Study was prematurely terminated due to visible particulates in placebo vials. Planned enrollment was 230 subjects.
†Subjects were asked to evaluate global evaluation of efficacy at bedtime using a 4-point categorical scale.
‡Overall P value derived from a statistical analysis of a 4-point categorical scale.
§Subjects were asked to evaluate the study treatments overall, using a 4-point categorical scale.

Hospital Performance Is an Increasingly Significant Focus for Health Professionals and Health Systems

- Pain
  - Establishing and maintaining an institutional pain performance improvement plan is a Joint Commission* requirement¹

- Patient satisfaction
  - Local, regional, or national patient satisfaction data are now being reported via Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS, also known as CAHPS® hospital survey)²

*Formerly known as the Joint Commission on Accreditation of Healthcare Organizations (JCAHO).

Safety and Tolerability of OFIRMEV™ (acetaminophen) injection
Clinical Trial Experience for OFIRMEV™ (acetaminophen) injection

Adult population

- A total of 1020 adult patients have received OFIRMEV in clinical trials, including 37.3% (n=380) who received 5 or more doses, and 17.0% (n=173) who received more than 10 doses
  - Most patients were treated with a dose of 1000 mg q6h. A total of 13.1% (n=134) received a dose of 650 mg q4h

- The most common adverse reactions in adult patients treated with OFIRMEV (incidence ≥5% and greater than placebo) were: nausea, vomiting, headache, and insomnia
Hepatic Safety Data for OFIRMEV™ (acetaminophen) injection

Peak ALT/AST value postbaseline: % of patients in all repeated-dose, placebo-controlled, all-adult studies*

<table>
<thead>
<tr>
<th></th>
<th>IV Acetaminophen (n=402)</th>
<th>Placebo (n=379)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT &gt;3x ULN</td>
<td>1.1% (n=4)</td>
<td>1.7% (n=6)</td>
</tr>
<tr>
<td>&gt;5x ULN</td>
<td>0.3% (n=1)</td>
<td>0.6% (n=2)</td>
</tr>
<tr>
<td>AST &gt;3x ULN</td>
<td>1.0% (n=4)</td>
<td>1.1% (n=4)</td>
</tr>
<tr>
<td>&gt;5x ULN</td>
<td>0.5% (n=2)</td>
<td>0.8% (n=3)</td>
</tr>
</tbody>
</table>

ALT=alanine aminotransferase; AST=aspartate aminotransferase.
*Data from a pooled analysis of 5 repeated-dose clinical studies involving adult patients.

Acetaminophen should be used with caution in patients with the following conditions: hepatic impairment or active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia, or severe renal impairment.

Treatment-Emergent Adverse Reactions Occurring ≥3% in OFIRMEV™ and at a Greater Frequency Than Placebo in Placebo-Controlled, Repeated-Dose Studies*

<table>
<thead>
<tr>
<th>System Organ Class – Preferred Term</th>
<th>OFIRMEV (N=402)</th>
<th>Placebo (N=379)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>138 (34)</td>
<td>119 (31)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>62 (15)</td>
<td>42 (11)</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia†</td>
<td>22 (5)</td>
<td>52 (14)</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>39 (10)</td>
<td>33 (9)</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>30 (7)</td>
<td>21 (5)</td>
</tr>
</tbody>
</table>

*Adult subjects only.
† Pyrexia adverse reaction frequency data is included in order to alert healthcare practitioners that the antipyretic effects of OFIRMEV may mask fever.

Safety Profile for IV Acetaminophen

- When dosed appropriately, OFIRMEV™ is not associated with the following adverse reactions
  - Respiratory depression
  - Sedation
  - Postoperative ileus
  - Cognitive impairment in older patients
  - Upper gastrointestinal bleeding
  - Surgical site bleeding
  - Renal toxicity
  - Platelet inhibition
  - Cardiovascular thrombotic events

- The most common adverse reactions in patients treated with OFIRMEV were nausea, vomiting, headache, and insomnia in adult patients and nausea, vomiting, constipation, pruritus, agitation, and atelectasis in pediatric patients
ED Admission

**Estimate time of ingestion**

- **Less than 4 hours since overdose**
  - **Less than 2 hours since overdose**
    - Gastric emptying
      - Activated charcoal
    - Draw blood plasma 4 hours after overdose for plasma acetaminophen assay
  - More than 2 hours since overdose
    - Activated charcoal
  - Acetaminophen concentration available within 8 hours of overdose
    - Wait for acetaminophen assay result
    - APAP level below risk line on nomogram
      - DC NAC if started
      - No further medical management needed
      - Treat other med or psychiatric problems
    - APAP level on or above risk line
      - Start NAC pending assay result
      - Loading does: 140 mg/kg
      - Treat with full course of NAC
      - Daily LFT's, prothrombin times
      - Provide supportive care

- **4 or more hours since overdose**
  - Draw blood ASAP for plasma acetaminophen assay
  - Acetaminophen concentration not available within 8 hours of overdose
    - Start NAC pending assay result
    - Loading does: 140 mg/kg
    - Treat with full course of NAC
    - Daily LFT’s, prothrombin times
    - Provide supportive care
Trivia Break: Got Brown Tree Snakes?
Brown Tree snakes (*Boiga irregularis*), native to eastern Indonesia, become invasive pests on Guam starting in the 1940's/1950's.

Without natural predators, the Brown Tree snake's population in Guam is estimated at upwards of 15,000 per square mile.

Have decimated certain native bird, bat, and reptile populations, as well as caused extensive economic losses (agriculture, pets, human bites, electric grid outages/repairs).

No safe and effective chemical-controls until discovery by USDA that acetaminophen (80 mg) will effectively kill Brown Tree snakes within 3 days of even a brief exposure to baited, dead mice.

Acute effects of larger doses of acetaminophen on local non-target species have not been detected.

# Recommended Dosing for Adults, Adolescents, and Children ≥2 Years Old

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dose Given Every 6 h*</th>
<th>Maximum Single Dose*</th>
<th>Maximum Total Daily Dose of Acetaminophen (by any route)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults and adolescents (≥13 years old) ≥50 kg</td>
<td>1000 mg</td>
<td>1000 mg</td>
<td>4000 mg in 24 h</td>
</tr>
<tr>
<td>Adults and adolescents (≥13 years old) &lt;50 kg</td>
<td>15 mg/kg</td>
<td>Weight-based dose: 15 mg/kg</td>
<td>75 mg/kg in 24 h</td>
</tr>
<tr>
<td>Children ≥2 to 12 years old</td>
<td></td>
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</tr>
</tbody>
</table>

- Adults and adolescents (≥13 years old) weighing ≥50 kg should receive a fixed dose regardless of body weight.
- The dose for adults and adolescents (≥13 years old) weighing <50 kg and children 2 to 12 years old should be calculated on the basis of body weight.
- Minimum dosing interval is Q4h.
- For instructions regarding Q4h dosing, please see full Prescribing Information.
- No dosage adjustment is required when transitioning to oral acetaminophen in adults and adolescents.
- OFIRMEV™ should be administered only as a 15-minute IV infusion. Administer only as directed.

**Administration of acetaminophen by any route in doses higher than recommended may result in hepatic injury, including the risk of severe hepatotoxicity and death.**

Abbreviation: Q4h, every 4 hours.

* Each mL contains 10 mg of OFIRMEV.

Summary of OFIRMEV™ (acetaminophen) injection

- Significant pain relief\(^1\)
- Reduced opioid consumption\(^1-4\)
  - Clinical benefit of reduced opioid consumption has not been demonstrated
- Improved patient satisfaction\(^1,2\)
- Established safety profile and well tolerated in clinical trials\(^1-5\)
- The first IV antipyretic approved for children \(\geq 2\) years of age
  - Fever reduction within 30 minutes noted for adults\(^2\)
  - The effectiveness of OFIRMEV for the treatment of acute pain and fever has not been studied in pediatric patients \(<2\) years old

Acetaminophen should be used with caution in patients with the following conditions: hepatic impairment or active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia, or severe renal impairment\(^5\)

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- The most common adverse reactions in patients treated with OFIRMEV were nausea, vomiting, headache, and insomnia in adult patients and nausea, vomiting, constipation, pruritus, agitation, and atelectasis in pediatric patients.
- The antipyretic effects of OFIRMEV may mask fever in patients treated for postsurgical pain.
- For additional product information, please see full Prescribing Information.
Case Presentation

- Pt. is a 37 year old female with a history of multiple episodes of PONV with past anesthetics.
- Presents for segmental mastectomy.
- Ofirmev 1GM IVPB administered in the pre-operative hold area followed by 2 mg midazolam prior to transport to OR.
- Induction was 160 mg propofol and 20 mg of ketamine with placement of a #3 pro-seal LMA.
Case Presentation

• Maintenance consisted of propofol 90-120 ug/kg/min and spontaneous ventilation with 60% FI02.

• Dexamethasone 6 mg was administered immediately following induction and 4 mg ondanesetron administered approximately 15 minutes prior to emergence for anti-emetic prophylaxis.
Case Presentation

- On request the surgeon infiltrated the surgical site with 20 cc of 1% lidocaine prior to incision and 20 cc of 0.5% bupivicaine at the surgical site at the completion of the surgery, approximately 1 ½ hours post induction.

- The propofol infusion was discontinued and the patient had a smooth emergence.
Case Presentation

• The patient was transported to the PACU in stable condition
• The patient reported a VAS of 0/10 in the PACU up until discharge to home 1 hour later and no complaints of nausea or episodes of emesis
• She was discharged with instructions to utilize PO acetaminophen 1 gm q 6 hours not to exceed 4 gms/24 hours
Case Presentation

• The patient was transported to the PACU in stable condition

• The patient reported a VAS of 0/10 in the PACU up until discharge to home 1 hour later and no complaints of nausea or episodes of emesis

• She was discharged with instructions to utilize PO acetaminophen 1 gm q 6 hours not to exceed 4 gms/24 hours
Case Presentation

• At 24 hour follow phone consult the patient reported complete satisfaction with her anesthetic and analgesic management with no episodes of nausea or episodes of emesis.
DOSAGE AND ADMINISTRATION:
- OFIRMEV may be given as a single or repeated dose. (2.1)
- OFIRMEV should be administered only as a 15-minute intravenous infusion. (2.4)

Adults and Adolescents Weighing 50 kg and Over:
- 1000 mg every 6 hours or 650 mg every 4 hours to a maximum of 4000 mg per day. Minimum dosing interval of 4 hours. (2.2)

Adults and Adolescents Weighing Under 50 kg:
- 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg per day. Minimum dosing interval of 4 hours. (2.2)

Children:
- Children ≥ 2 to 12 years old: 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg per day. Minimum dosing interval of 4 hours. (2.3)
Questions
The Blood Brain Barrier: Functional Divisions