Perioperative Pain Management: The Role of IV Acetaminophen

Chris Pasero, MS, RN-BC, FAAN
September 14, 2012

Acute Perioperative Pain

- Acute pain is extremely common
  - Perioperative pain
    - Approximately 46 million inpatient procedures and 35 million outpatient surgeries were performed in the US in 2006
    - Despite new treatment standards, guidelines, and educational efforts, acute postoperative pain continues to be undertreated, with up to 75% of patients in the US still failing to receive adequate postoperative pain relief

Postoperative Pain Management Did Not Improve from 1995 to 2003

Overall Pain After Surgery

- 1995 (N=100)
- 2003 (N=250)

<table>
<thead>
<tr>
<th>Pain Level</th>
<th>1995</th>
<th>2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slight</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Moderate</td>
<td>28</td>
<td>33</td>
</tr>
<tr>
<td>Severe</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Extreme</td>
<td>8</td>
<td>3</td>
</tr>
</tbody>
</table>
**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 effects (reduced opioid-related adverse events) can be achieved via the use of non-opioid agents and regional blocks
- ASA Task Force Recommendations:
  - Unless contraindicated, all patients should receive an around-the-clock regimen of a non-opioid agent
    - NSAIDs
    - COXIBs
    - Acetaminophen
  - Consider supplemental regional anesthesia techniques

**ASPMN Recommendations for Multimodal Analgesia**

- Nurses should act as strong advocates for pain management plans that incorporate opioid dose-sparing strategies initiated early in the course of treatment:
  - On admission
  - Before surgery
  - During surgery
  - Early after surgery
- Multimodal analgesic therapy that combines opioids with other analgesics has proven efficacy:
  - Acetaminophen
  - NSAIDs
  - Anticonvulsants

**Multimodal Approach to Analgesia**
The Historical Acute Pain Paradigm

- Severe Pain
  - +++
  - Opioids
- Moderate Pain
  - ++
  - Opioids
- Mild Pain
  - +
  - Opioids

Opioids

+++ Opioids

Mild Pain
Moderate Pain
Severe Pain

STEP 1
STEP 2
STEP 3

Multimodal Approach to Acute Pain Management

- Severe Pain
  - STEP 1
  - Higher doses of opioids
- Moderate Pain
  - STEP 1
  - Low doses of opioids
  - STEP 2
  - Acetaminophen, NSAIDs, or COXIBs
  - Local/regional anesthesia
- Mild Pain

Pain and Patient Satisfaction May Affect Hospital Reimbursement

- Pain
  - Establishing and maintaining an institutional pain performance improvement plan is a Joint Commission requirement.
- 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).
  - As part of the Affordable Care Act 2010, the Centers for Medicare and Medicaid (CMS) have established hospital reimbursement based on HCAHPS scores.

- As of the Affordable Care Act 2010, the Centers for Medicare and Medicaid Services (CMS) have established hospital reimbursement based on HCAHPS scores.
OFIRMEV® (acetaminophen) Injection Overview

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

OFIRMEV is approved for use in adults and children 2 years of age and older.

OFIRMEV® Utilization
- More than 400 million doses of IV acetaminophen have been distributed in over 50 countries worldwide

More than 1400 US Hospitals with OFIRMEV on Formulary (through Oct-2011)
Important Safety Information for OFIRMEV® (acetaminophen) Injection

- Administer only as a 15-minute infusion
- Do not exceed the maximum recommended daily dose of acetaminophen
- Exceeding the maximum daily dose of acetaminophen by any route may result in hepatic injury, including the risk of severe hepatotoxicity and death
- Contraindicated in patients with severe hepatic impairment, severe active liver disease, or with known hypersensitivity to acetaminophen or excipients in the formulation
- Use with caution in patients with hepatic impairment or active hepatic disease, chronic malnutrition, severe hypovolemia, or severe renal impairment
- Discontinue immediately if symptoms associated with allergy or hypersensitivity occur
- Most common adverse reactions in adult patients: nausea, vomiting, headache, and insomnia
- Most common adverse reactions in pediatric patients: nausea, vomiting, constipation, pruritus, agitation, and atelectasis
- Antipyretic effects may mask fever in patients treated for post-surgical pain
- For additional product information, please see full Prescribing Information

Pharmacodynamics of OFIRMEV®

- Rapid onset of action:
  - Statistically significant improvement within 15 minutes of administration for both pain and fever
  - Measurable CSF levels at 15 minutes
- Peak effect: within an hour of administration
- Duration of effect: 4 to 6 hours
- No significant effect on platelet aggregation

Study of Acetaminophen Plasma Pharmacokinetics (IV, PO, PR)

(Singla et al., 2011)

Randomized, 3-way, cross-over design in 6 healthy volunteers; efficacy was not assessed

<table>
<thead>
<tr>
<th>Mean Plasma Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen 1g</td>
</tr>
<tr>
<td>Acetaminophen 1g</td>
</tr>
<tr>
<td>Acetaminophen 1g</td>
</tr>
</tbody>
</table>

- The IV route produced a 76% higher mean plasma Cmax (p = 0.0004) than PO, and 256% higher (p < 0.0001) than PR
- The median plasma Tmax for the IV route was earlier (0.29h) than PO (1.0h, p = 0.0019) or PR (2.5h, p = 0.0065)
The mean CSF IV acetaminophen AUC over 6h is 75% higher than the PO group (p = 0.0099) and 142% higher than the PR group (p = 0.0004).

Comparing mean CSF Cmax values, the IV group was 59.7% higher than PO (p < 0.0001) and 86.8% higher than PR (p < 0.0001).

The median CSF Tmax values were 2.0, 4.0 and 6.0h for IV, PO and PR, respectively.

---

**Oral Absorption of Acetaminophen Can Be Reduced by Preoperative Fasting and Stress**

- Study of patients undergoing orthopedic or ENT surgery (n=106)
  - Oral acetaminophen 30 minutes prior to induction (n=52)
  - IV acetaminophen immediately prior to induction (n=54)
- Plasma samples taken at 30 minutes post-dose and every 30 minutes for 4h
- Conclusion: IV acetaminophen gave higher and more reliable plasma concentrations than oral.

---

**Absorption of Oral Acetaminophen May be Decreased by Postoperative Stress and Opioids**

- Patients received IM morphine 10 mg upon first complaint of pain post-op
- Oral acetaminophen solution 20 mg/kg given:
  - at least 12 hours pre-op, and
  - 30 minutes after morphine administration
- Results:
  - Administration of morphine reduced and delayed oral acetaminophen absorption

---

Metabolism of OFIRMEV®

- Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves 3 principal separate pathways:
  - Glucuronidation
  - Sulfation
  - Oxidation
- IV acetaminophen bypasses first-pass liver exposure and metabolism.
Study in Major Orthopedic Surgery (Sinatra et al., 2005), cont.

- IV acetaminophen 1 g q6h + PCA morphine (n=49)
- Placebo q6h + PCA morphine (n=52)

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>IV Acetaminophen</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>00</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>01</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>02</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>03</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>04</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>05</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>06</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>07</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>08</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>09</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

Patient satisfaction: good to excellent at 24 h 40.8% 23.1% 0.004 †
Median time to first use of rescue 3.0 h 0.8 h 0.0001
Morphine consumption over 24 h‡ 38.3 mg (33% <0.01)
Safety (adverse reactions) IV acetaminophen is comparable to placebo

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

2. Data on file, Cadence Pharmaceuticals, Inc.

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 (pain intensity differences) 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 after abdominal laparoscopic surgery


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

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

Reduced Opioid Consumption

<table>
<thead>
<tr>
<th>Procedure Type</th>
<th>Total Hip &amp; Knee Replacement</th>
<th>Major Abdominal Surgery*</th>
<th>Total Hip Replacement**</th>
<th>Adult Total Hip &amp; Knee Replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>38.4</td>
<td>138</td>
<td>6.6</td>
<td>87</td>
</tr>
<tr>
<td>OFIRMEV</td>
<td>36.3</td>
<td>45</td>
<td>4.5</td>
<td>67</td>
</tr>
</tbody>
</table>

Note: Opioid consumption reduction is highly dependent on clinical trial design, and the clinical consequence of any amount of opioid consumption reduction may not have been evaluated or demonstrated in a given trial.

Improved Patient Satisfaction

<table>
<thead>
<tr>
<th>Procedure Type</th>
<th>% of Patients Reporting “Good” or “Excellent” Satisfaction</th>
<th>% of Patients Reporting “Good” or “Excellent” Satisfaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Laparoscopy</td>
<td>93.9%</td>
<td>88.9%</td>
</tr>
<tr>
<td>Total Hip &amp; Knee Replacement</td>
<td>91.6%</td>
<td>86.9%</td>
</tr>
<tr>
<td>Total Hip Replacement**</td>
<td>88.0%</td>
<td>82.3%</td>
</tr>
</tbody>
</table>

All patients had access to IV opioid rescue medication as needed. Patient satisfaction was a pre-specified secondary endpoint where subjects were asked to evaluate the study treatments overall using a 4-point categorical scale.

*This study was terminated early due to the detection of particulates in some placebo vials.

Laparoscopic Hysterectomy Case Study Patient Y: Case Description

- **History & Physical**
  - 42yo G4P2A2 female with a 2 year history of ironing menorrhagia and dysmenorrhea
  - Patient requests definitive surgical correction and cervical preservation
  - On the pelvic examination, a 14-week sized uterus was palpated
  - Pelvic ultrasound revealed an enlarged uterus with multiple fibroids

- **Diagnosis**
- Symptomatic uterine fibroids

- **Recommended Procedure Type**
- Laparoscopic supracervical hysterectomy

*This study was terminated early due to the detection of particulates in some placebo vials.*
### Perioperative Analgesic Protocol

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>PreOp</th>
<th>IntraOp</th>
<th>PostOp Day 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen injection</td>
<td>1 g</td>
<td></td>
<td>1 g q8h for 24 hours</td>
</tr>
<tr>
<td>% ketorolac</td>
<td>150 mg bolus</td>
<td>50 mg (IV) bolus</td>
<td></td>
</tr>
<tr>
<td>% ketorolac</td>
<td>30 mg (or end of case once temazepam dosed)</td>
<td>30 mg q6h for 24 hours</td>
<td></td>
</tr>
<tr>
<td>% oxycodone</td>
<td>3 mg b.i.d</td>
<td>q6h pm for breakthrough pain</td>
<td></td>
</tr>
<tr>
<td>PO oxycodone</td>
<td></td>
<td></td>
<td>5-10 mg q6h pm</td>
</tr>
</tbody>
</table>

### Pain Assessment

- **PACU**: 4-5/10 pain
- **POD 0**: 3/10 pain later that day at rest
- **POD 1**: 5/10 pain with first ambulation in the morning
- **POD 1**: 2-3/10 pain at time of discharge

### Opioid Consumption

- **POD 1**: Total of 30 mg of PO oxycodone consumed (5-10 mg q6h pm)
- **POD 1**: IV morphine available prn for breakthrough pain but not utilized

### Patient Satisfaction

- "Excellent" rating for pain control on a 4-point categorical scale

---

### Outcomes

- **Pain Assessment**
  - PACU: 4-5/10 pain
  - POD 0: 3/10 pain later that day at rest
  - POD 1: 5/10 pain with first ambulation in the morning
  - POD 1: 2-3/10 pain at time of discharge
- **Opioid Consumption**
  - POD 1: Total of 30 mg of PO oxycodone consumed (5-10 mg q6h pm)
  - POD 1: IV morphine available prn for breakthrough pain but not utilized
- **Patient Satisfaction**
  - "Excellent" rating for pain control on a 4-point categorical scale

### Observations

- **Ambulation**
  - Foley catheter removed 6 hours after surgery
  - Patient up and around room/bathroom the evening of the procedure
  - Patient walking in hallway the morning of POD 1
- **Discharge**
  - Patient discharged 24 hours after procedure

---

Please see full Prescribing information for complete safety information.
Laparoscopic Colectomy Case Study Patient X:
Case Description

- **History & Physical**
  - 35 yr old male with 3 month history of crampy abdominal pain, bleeding per rectum and 10 lbs unintentional weight loss
  - Previous open appendectomy and repair of a congenitally rotated kidney
  - No FH of colorectal cancer or IBD
  - No abnormalities on physical exam

Case Contributed by: Dr. Christopher Mantyh, Director, Colorectal Surgery, Critical Care, Duke University, Durham, NC

This case study is intended only to provide healthcare professionals with an example of the use of OFIRMEV® (acetaminophen) injection in the treatment of one specific patient. The outcomes described may not be representative of, and may differ significantly from, outcomes that may be obtained in treating other patients. This case study is not intended to provide specific treatment advice, recommendations or opinions, and should not replace a clinician’s judgment with respect to the treatment of any particular patient.

- **Tests**
  - Colonoscopy: biopsy confirmed sigmoid adenocarcinoma, remainder of colon normal
  - CT: thickened sigmoid colon, no visible metastasis
  - CEA: 2.1 ng/mL

- **Diagnosis**
  - Sigmoid colon cancer

- **Recommended procedure**
  - Laparoscopic sigmoid resection (laparoscopic low anterior resection, splenic flexure takedown, colorectal anastomosis, proctoscopy)

---

Laparoscopic Colectomy Case Study Patient X:
Perioperative Analgesic Protocol

<table>
<thead>
<tr>
<th>NITROFUS® (acetaminophen) injection</th>
<th>IV</th>
<th>PCA</th>
<th>IV</th>
<th>PCA</th>
<th>IV</th>
<th>PCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 g (max=3)</td>
<td>1</td>
<td>1/8</td>
<td>1/8</td>
<td>1/8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV naltrexone</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV hydromorphone</td>
<td>500</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intronic z Medication (continuous i.v. for 24 hours)</td>
<td>of</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 mg sodium citrate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 mg metoclopride</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg naltrexone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg hydromorphone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg morphine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 mg atropine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes:
- Lidocaine 5% patch is indicated for post-herpetic neuralgia only
- Do not exceed the maximum total daily dose of acetaminophen of 4 g
Laparoscopic Colectomy Case Study Patient X: Outcomes

- **Pain Assessment**
  - Initial PACU Score: 6/10 pain
  - Discharge PACU Score: 3/10 pain
  - POD 1 Score: 4/10 pain (3 mL bolus of epidural given)
  - POD 2 Score: 0/10 pain
  - POD 3 Score: 1/10 pain
- **Opioid Consumption**
  - POD 1: epidural + 3 mL bolus for breakthrough pain
  - POD 2: epidural
  - POD 3: 20 mg PO oxycodone (5 mg q4h prn)
- **Patient Satisfaction**
  - POD 1-3: “Good-excellent” rating for pain control on a 3-point categorical scale

* Based on 10-point numeric rating scale (NRS)

Laparoscopic Colectomy Case Study Patient X: Observations

- **Ambulation/Diet**
  - POD 1: ambulating, clear liquids for breakfast, regular diet for dinner
  - POD 2: + flatus/BM, tolerating regular diet, foley catheter removed when epidural out
- **Discharge**
  - PACU Discharge Time: 2 hours and 3 minutes
  - Hospital Length of Stay: 3 days
  - Discharge medications:
    - Acetaminophen 975 mg PO q6h prn
    - Oxycodone 5-10 mg q3h prn
    - Enoxaparin 40 mg subcutaneously daily for a week
- **Follow-up**
  - Pathology: T3N1M0 tumor, 6.2x5.4x1.2 cm, 3/28 LN +, will receive 6 months of adjuvant chemotherapy
  - Surgical clinic visit 4 weeks post D/C: all wounds well healed, tolerating regular diet, 2 BM/day, no further bleeding or abdominal pain, Hct normalizing

Safety and Tolerability of **OFIRMEV®** (acetaminophen) Injection

Please see full Prescribing information for complete safety information
Clinical Trial Experience for OFIRMEV®

Adult population

- A total of 1020 adult patients have received OFIRMEV in clinical trials supporting approval, including 37.3% (n=380) who received 5 or more doses, and 17.0% (n=173) who received more than 10 doses.
- 36.9% (n=380) patients received a dose of 1000 mg q6h.
- 13.1% (n=134) received a dose of 650 mg q4h.
- Patients received OFIRMEV for up to 7 days.

Hepatic Safety Data for OFIRMEV®

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

<table>
<thead>
<tr>
<th>IV Acetaminophen</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td></td>
</tr>
<tr>
<td>≤ 5 x ULN</td>
<td>1.1% (n=402)</td>
</tr>
<tr>
<td>&gt; 5 x ULN</td>
<td>0.1% (n=402)</td>
</tr>
<tr>
<td>AST</td>
<td></td>
</tr>
<tr>
<td>≤ 5 x ULN</td>
<td>1.2% (n=402)</td>
</tr>
<tr>
<td>&gt; 5 x ULN</td>
<td>0.6% (n=402)</td>
</tr>
</tbody>
</table>

*Data from a pooled analysis of 5 repeated-dose placebo-controlled clinical studies in adult patients.

Acetaminophen is contraindicated in patients with severe hepatic impairment or severe active liver disease and should be used with caution in patients with hepatic impairment or active liver disease.

Treatment-Emergent Adverse Events Occurring ≥ 3% in Adults Receiving OFIRMEV® and at a Greater Frequency Than Placebo in Repeated-Dose Studies

<table>
<thead>
<tr>
<th>Treatment-Emergent Adverse Event (TEAE)</th>
<th>OFIRMEV (N=402)</th>
<th>Placebo (N=379)</th>
</tr>
</thead>
<tbody>
<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>Pyrexia†</td>
<td>22 (5%)</td>
<td>10 (3%)</td>
</tr>
<tr>
<td>Headache</td>
<td>39 (10%)</td>
<td>33 (9%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>38 (7%)</td>
<td>21 (6%)</td>
</tr>
</tbody>
</table>

† Pyrexia adverse reaction frequency data is included in order to alert healthcare practitioners that the antipyretic effects of OFIRMEV may mask fever. The differences between treatment groups were not statistically significant for any reported TEAE.
Safety Profile for OFIRMEV®

In clinical trials consisting of 1,375 patients, OFIRMEV was not associated with the following side effects:

- Respiratory depression
- Sedation
- Postoperative nausea
- Cognitive impairment
- Upper gastrointestinal bleeding
- Surgical site bleeding
- Renal toxicity
- Platelet inhibition
- Cardiovascular thrombotic events
- Postoperative ileus
- Platelet inhibition
- Cognitive impairment
- Cardiovascular thrombotic events
- Upper gastrointestinal bleeding

OFIRMEV® (acetaminophen) Injection
1000 mg/100 mL (10 mg/mL)

- A sterile, clear, colorless, non-pyrogenic, isotonic formulation
- For IV administration only
- For single use only
- Each vial contains 100 mL with:
  - Acetaminophen 1000 mg
  - Mannitol 3850 mg
  - Cysteine hydrochloride monohydrate 25 mg
  - Sodium phosphate 10.4 mg
- Osmolality ~290 mOsm/kg and pH ~5.5
- Administered only as a 15-minute intravenous infusion within 6 hours of opening (preservative-free)

Suggested Dosing of OFIRMEV®

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dose Given Every 6h*</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 24h</td>
</tr>
<tr>
<td>Adults and adolescents ≥13 years old ≤50 kg</td>
<td>15 mg/kg</td>
<td>15 mg/kg</td>
<td>75 mg/kg in 24h</td>
</tr>
<tr>
<td>Children 2 to 12 years old</td>
<td>15 mg/kg</td>
<td>15 mg/kg</td>
<td>75 mg/kg in 24h</td>
</tr>
</tbody>
</table>

* Each mL contains 10 mg of OFIRMEV.

Administration of acetaminophen by any route at doses higher than recommended may result in hepatic injury, including the risk of severe hepatotoxicity, potentially resulting in liver failure, with or without fulminant hepatic failure, and death.

OFIRMEV® is not approved for use in patients <2 years of age.

For instructions regarding q4h dosing, please see full Prescribing Information for OFIRMEV.
**Administration of OFIRMEV®**

- OFIRMEV should be administered only as a 15-minute IV infusion.
- Minimum dosing interval is 4 hours, not to exceed 4 g in 24 hours.
- An infusion pump is not required except when delivering weight-based calculated doses less than 600 mg (60 mL).
- Use a syringe pump for administering small volume doses, particularly in young children.
- No dosage adjustment is required when transitioning to oral acetaminophen.
- Administer only as directed.

---

**Perioperative Dosing Scenarios**

The following clinical scenarios are examples of OFIRMEV dosing intervals but are not intended to replace the dosing instructions included in the product labeling.

**OFIRMEV® dosing schedule by surgery duration**

<table>
<thead>
<tr>
<th>Point of care</th>
<th>PreOp</th>
<th>IntraOp</th>
<th>PostOp</th>
<th>PACU / PostOp</th>
<th>Surgical Floor or Step Down Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of administration</td>
<td>0.5–1 h (pre-surgery)</td>
<td>≤1 h</td>
<td>2–4 h</td>
<td>≥5 h</td>
<td>≥90 min</td>
</tr>
<tr>
<td>Inpatient:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long procedure</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Short procedure</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Trauma</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Outpatient:</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

*Indicates approximate duration of surgery*

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

---

**Summary of OFIRMEV® Data**

- Significant pain relief
- Reduced opioid consumption
- Improved patient satisfaction
- Established safety profile and well tolerated in clinical trials
- Utilization considerations
  - Early initiation (pre-operative; intra-operative)
  - Schedule q6h or for as long as clinically warranted

---

Information 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.
Important Safety Information for OFIRMEV® (acetaminophen) Injection

- Administer only as a 15-minute infusion
- Do not exceed the maximum recommended daily dose of acetaminophen
- Exceeding the maximum daily dose of acetaminophen by any route may result in hepatic injury, including the risk of severe hepatotoxicity and death
- Contraindicated in patients with severe hepatic impairment, severe active liver disease, or with known hypersensitivity to acetaminophen or excipients in the formulation
- Use with caution in patients with hepatic impairment or active hepatic disease, cirrhosis, alcoholism, severe hypovolemia, or severe renal impairment
- Discontinue immediately if symptoms associated with allergy or hypersensitivity occur
- Most common adverse reactions in adult patients: nausea, vomiting, headache, and abdominal pain
- Most common adverse reactions in pediatric patients: nausea, vomiting, abdominal pain, diarrhea, and headache
- Antipyretic effects may mask fever in patients treated for post-surgical pain
- For additional product information, please see full Prescribing Information