Laparoscopic hysterectomy
Craig Saffer, MD, Obstetrician and Gynecologist, West Coast OB/GYN, San Diego, CA

CASE PRESENTATION
A 42-year-old, G4P2A2 female presented with a history of menorrhagia and dysmenorrhea for the past 2 years. Patient reported worsening symptoms and requested definitive surgical correction and cervical preservation.

On the pelvic examination, a 14-week-sized uterus was palpated. Patient underwent a pelvic ultrasound, which revealed an enlarged uterus with multiple fibroids.

DIAGNOSIS AND RECOMMENDED PROCEDURE
• Symptomatic uterine fibroids
• Laparoscopic supracervical hysterectomy

PATIENT’S PERIOPERATIVE ANALGESIC TREATMENT PROTOCOL

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>PreOp</th>
<th>IntraOp</th>
<th>PostOp Day 1†</th>
</tr>
</thead>
<tbody>
<tr>
<td>OFIRMEV® (acetaminophen) injection</td>
<td>1 g (pre-incision)</td>
<td>1 g q6h for 24 hours</td>
<td></td>
</tr>
<tr>
<td>IV fentanyl</td>
<td>100 μg (induction)</td>
<td>50 μg (extubation)</td>
<td></td>
</tr>
<tr>
<td>IV ketorolac</td>
<td>30 mg (at end of case once hemostasis assured)</td>
<td>30 mg q6h for 24 hours</td>
<td></td>
</tr>
<tr>
<td>IV morphine</td>
<td>2 mg q2h prn (none administered)</td>
<td>2 mg q2h prn (none administered)</td>
<td></td>
</tr>
<tr>
<td>PO oxycodone</td>
<td></td>
<td>5-10 mg q3h prn</td>
<td></td>
</tr>
</tbody>
</table>

†PostOp Day 1 defined as 0–24 h after surgery.
• Do not exceed the recommended maximum daily limits of acetaminophen by all routes

INDICATIONS AND USAGE
OFIRMEV® (acetaminophen) injection is indicated for the management of mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics, and reduction of fever.

IMPORTANT RISK INFORMATION
WARNING: RISK OF MEDICATION ERRORS AND HEPATOTOXICITY
Take care when prescribing, preparing, and administering OFIRMEV Injection to avoid dosing errors which could result in accidental overdose and death. In particular, be careful to ensure that:
• the dose in milligrams (mg) and milliliters (mL) is not confused;
• the dosing is based on weight for patients under 50 kg;
• infusion pumps are properly programmed; and
• the total daily dose of acetaminophen from all sources does not exceed maximum daily limits.

OFIRMEV contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed the recommended maximum daily limits, and often involve more than one acetaminophen-containing product.

Please see additional Important Risk Information on reverse and in accompanying Full Prescribing Information.

* 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.
**PostOp Outcomes**

<table>
<thead>
<tr>
<th>PAIN ASSESSMENT*</th>
<th>OPIOID CONSUMPTION</th>
<th>PATIENT SATISFACTION</th>
</tr>
</thead>
</table>
| • In PACU: 4–5/10 decreased to 3/10 | • PostOp Day 1:  
  - Total 30 mg PO oxycodone consumed (5–10 mg q3h prn)  
  - IV morphine available prn for breakthrough pain but none administered | • “Excellent” rating for pain control on a 4-point categorical scale |
| • PostOp Day 1: 5/10 with first ambulation decreased to 2–3/10 at discharge | |

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

**PATIENT AMBULATION/DISCHARGE**
The foley catheter was removed 6 hours after surgery. The patient was up and around the room and bathroom the evening of the procedure, and walking in the hallways the morning of PostOp Day 1. She was discharged 24 hours after the procedure.

**IMPORTANT RISK INFORMATION**

**CONTRAINDICATIONS**
- Acetaminophen is contraindicated in patients with:
  - known hypersensitivity to acetaminophen or to any of the excipients in the intravenous (IV) formulation.
  - severe hepatic impairment or severe active liver disease.

**WARNINGS AND PRECAUTIONS**
- Administration of acetaminophen in doses higher than recommended may result in hepatic injury, including the risk of liver failure and death. Do not exceed the maximum recommended daily dose of acetaminophen. The maximum recommended daily dose of acetaminophen includes all routes of acetaminophen administration and all acetaminophen-containing products administered, including combination products. Dosing errors could result in accidental overdose and death.
- Use caution when administering acetaminophen in patients with the following conditions: hepatic impairment or active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia (e.g., due to dehydration or blood loss), or severe renal impairment (creatinine clearance \( \leq 30 \text{ mL/min} \)).
- Rarely, acetaminophen may cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Hypersensitivity and anaphylaxis associated with the use of acetaminophen have been reported. Clinical signs included swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, and pruritus. The antipyretic effects of OFIRMEV may mask fever.
- **Serious adverse reactions** may include hepatic injury, serious skin reactions, hypersensitivity, and anaphylaxis. Common adverse reactions in adults include nausea, vomiting, headache, and insomnia. Common adverse reactions in pediatric patients include nausea, vomiting, constipation, pruritus, agitation, and atelectasis.

**USE IN SPECIFIC POPULATIONS**
- Pregnancy: Pregnancy Category C. OFIRMEV should be given to a pregnant woman only if clearly needed.
- Breast Feeding: While studies with OFIRMEV have not been conducted, acetaminophen is secreted in human milk in small quantities after oral administration.
- Pediatrics: The effectiveness of OFIRMEV for the treatment of acute pain and fever has not been studied in pediatric patients < 2 years of age.

Please see additional Important Risk Information, including boxed warning, on reverse side and in accompanying Full Prescribing Information.
OFIRMEV®

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Indications and Usage
OFIRMEV® (acetaminophen) injection is indicated for:

- Management of mild to moderate pain
- Management of fever

Contraindications
OFIRMEV® is contraindicated in patients with:

- Hypersensitivity to acetaminophen

Warnings and Precautions

- Use cautiously in patients with hepatic impairment or hepatic disease
- Use with caution in patients with renal impairment

Adverse Reactions

- The most common adverse reactions in patients treated with OFIRMEV were nausea, vomiting, headache, and dizziness in adult patients
- The most common adverse reactions in pediatric patients were nausea, vomiting, headache, and dizziness

OVERDOSAGE

- The most common adverse reactions in patients treated with OFIRMEV were nausea, vomiting, headache, and dizziness

References

- Full prescribing information is available at www.fda.gov/medwatch

Additional information, including the complete prescribing information, is available at www.fda.gov/medwatch
There are no adequate and well-controlled studies with doses of acetaminophen up to 6000 ppm. Female rats demonstrated an equivocal evidence of carcinogenic activity based on increased incidences of mononuclear cell leukemia at 24 times the maximum human daily dose (MHDD) of 4g/day, based on a body surface area comparison. In contrast, there was no evidence of carcinogenic activity in male rats (3.7 times the MHDD, based on a body surface area comparison).

Acetaminophen was not mutagenic in the bacterial reverse mutation assay (Ames test). In contrast, acetaminophen testicular toxicity at doses of up to 6000 ppm. Female rats demonstrated a clear dose-related increase in the frequency of chromosomal aberrations in human lymphocytes. Although testicular toxicity was dose-related, the effect did not become clastogenic when administered at a dose of 1500 mg/kg/day of acetaminophen exposure (based on a body surface area comparison). In contrast, no clastogenicity was noted at a dose of 1500 mg/kg/day (5.4 times the MHDD, based on a body surface area comparison).

There is one well-documented report of a rash in a breast-fed infant after maternal ingestion of acetaminophen. In a single case report of a 3-month-old breast-fed infant, a case of acetaminophen overdose was suspected, but an adequate serum acetaminophen assay could not be performed. In a single-dose, endotoxin-induced fever study in 60 healthy volunteers, patients receiving OFIRMEV 1000 mg every 6 hours or 650 mg every 12 hours for 24 hours versus placebo in the treatment of 244 patients with moderate to severe postoperative abdominal laparoscopic surgery. Patients receiving OFIRMEV experienced a statistically significant greater reduction in pain intensity over 24 hours compared to placebo.

Acetaminophen is mainly metabolized in the liver by first-order kinetics and involves three principal pathways: conjugation with glucuronic acid, with sulfa-tide, and oxidation via the cytochrome P450 enzymes pathway, primarily involving CYP2E1, a reactive intermediate metabolite (N-acetyl-p-benzoquinone imine or NAPQI). NAPQI can cause oxidative damage to liver cells by undergoing rapid conjugation with glutathione and is then further metabolized to form systemically inactive glutathione conjugates.

The efficacy of OFIRMEV 1000 mg in the treatment of adult fever was evaluated in an randomized, double-blind, placebo-controlled clinical trial. The study was a 6-hour, single-dose, endotoxin-induced fever study in 60 healthy adult males. A statistically significant antipyretic effect of OFIRMEV was demonstrated in both children and adults.

11. DESCRIPTION

Acetaminophen is a non-salicylate and non-steroidal analgesic and antipyretic agent. Its chemical name is N-acetyl-p-aminophenol. It has a molecular weight of 151.16. Its structural formula is:

\[ \text{C}_{8}\text{H}_{9}\text{NO}_2 \]

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism of the analgesic and antipyretic properties of acetaminophen is not established but is thought to involve the inhibition of prostaglandin synthesis.

12.2 Pharmacodynamics

Acetaminophen has been shown to have analgesic and antipyretic activities in animal and human studies. Single doses of OFIRMEV up to 3000 mg and repeated doses of 1000 mg every 4 hours for 48 hours have not been shown to cause a significant effect on platelet aggregation. However, in vitro studies have shown no or minimal changes in bleeding time after receiving multiple doses of acetaminophen.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in mice and rats have been completed by the National Toxicology Program to evaluate the carcinogenic potential of acetaminophen. In two feeding studies, F344/N rats and B6C3F1 mice were fed a diet containing acetaminophen up to 6000 ppm. Female rats demonstrated a clear dose-related increase in the frequency of chromosomal aberrations in human lymphocytes. Although testicular toxicity was dose-related, the effect did not become clastogenic when administered at a dose of 1500 mg/kg/day (3.6-times the MHDD, based on a body surface area comparison). In contrast, no clastogenicity was noted at a dose of 750 mg/kg/day (6.5 times the MHDD, based on a body surface area comparison).

14.3 Pediatric Acute Pain and Fever

OFIRMEV was studied in 315 pediatric patients in two active-controlled, placebo-controlled, and pharmacokinetic trials (see in Specific Populations (4.6).

14.4 Pediatric Use

Pain Study 2 evaluated the analgesic efficacy of repeated doses of OFIRMEV 1000 mg every 6 hours or 650 mg every 12 hours for 24 hours versus placebo in the treatment of 244 patients with moderate to severe postoperative abdominal laparoscopic surgery. Patients receiving OFIRMEV experienced a statistically significant greater reduction in pain intensity over 24 hours compared to placebo.

In a single-dose, endotoxin-induced fever study in 60 healthy adult males. A statistically significant antipyretic effect of OFIRMEV was demonstrated in both children and adults.