Laminectomy

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CASE PRESENTATION
A 31-year-old, 72 kg female with history (~1 month) of back pain and right lower extremity pain presented to the ER with worsening pain and foot numbness and was subsequently admitted. The patient had no relevant past medical history and surgical history consisted of left ankle surgery, C-section and breast reduction. The patient had no known drug allergies. Concomitant medications prior to admission included oral acetaminophen.

Test Results:
• MRI: Large right L5-S1 herniated nucleus pulposus

DIAGNOSIS AND RECOMMENDED PROCEDURE
• Right L5-S1 laminectomy

PATIENT’S PERIOPERATIVE ANALGESIC PROTOCOL

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>IntraOp</th>
<th>PACU</th>
<th>PostOp Day 0</th>
<th>PostOp Day 1</th>
<th>PostOp Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>OFIRMEV® (acetaminophen) injection</td>
<td>1 g (One dose prior to incision)</td>
<td></td>
<td>1 g q6h for 24h (Three doses given on the floor)</td>
<td>1 g q6h for 24h (One dose)</td>
<td></td>
</tr>
<tr>
<td>IV fentanyl</td>
<td>200 μg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV ketamine†</td>
<td>20 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV dexamethasone</td>
<td>4 mg</td>
<td></td>
<td>4 mg</td>
<td>4 mg</td>
<td></td>
</tr>
<tr>
<td>IV magnesium sulfate‡</td>
<td>2 g</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV hydromorphone</td>
<td>300 μg</td>
<td>300 μg</td>
<td>300 μg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV ketorolac</td>
<td></td>
<td></td>
<td></td>
<td>7.5 mg</td>
<td>7.5 mg</td>
</tr>
</tbody>
</table>

† Ketamine is indicated for anesthesia only
‡ Magnesium sulfate is not FDA approved for use as an analgesic
• Do not exceed the recommended maximum daily limits of acetaminophen by all routes

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>
</tr>
</thead>
<tbody>
<tr>
<td>PACU: 2/10</td>
<td>PACU: 300 μg hydromorphone</td>
</tr>
<tr>
<td>PostOp Day 1: 4/10</td>
<td>PostOp Day 0: 300 μg hydromorphone</td>
</tr>
<tr>
<td></td>
<td>PostOp Day 1: 300 μg hydromorphone</td>
</tr>
<tr>
<td></td>
<td>PostOp Day 2: none</td>
</tr>
</tbody>
</table>

*Based on a 10-point visual analog scale (VAS).

**PATIENT DISCHARGE**

- The patient was discharged from the PACU after 55 minutes.
- The total hospital length of stay was 3 days. Patient was discharged in the morning on PostOp Day 2 due to transportation issues on PostOp Day 1.
- Follow-up physical therapy visits was scheduled 3 x weekly. A follow up office visit was scheduled for 2 weeks PostOp.

**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 ≤ 30 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 (acetaminophen) Injection**

**INDICATIONS AND USAGE**

OFIRMEV (acetaminophen) injection is indicated for:

- The management of mild to moderate pain in adults and pediatric patients aged 2 to 12 years.
- The reduction of fever in adults and in pediatric patients aged 2 to 12 years.

**CONTRAINDICATIONS**

Acetaminophen is contraindicated in:

- Patients with known hypersensitivity to acetaminophen.
- Patients with known hypersensitivity to ingredients in the formulation.

**WARNINGS AND PRECAUTIONS**

- Patients with severe hepatic impairment or severe active liver disease.
- Patients with known or suspected acetaminophen allergy.
- Patients with severe renal dysfunction or severe acidosis.

**ADVERSE REACTIONS**

Adverse reactions associated with the use of OFIRMEV include:

- Skin disorders: Rash, pruritus, urticaria.
- Hepatic disorders: Liver failure, hepatotoxicity.
- Gastrointestinal disorders: Diarrhea, abdominal pain.
- Respiratory disorders: Atelectasis.
- Psychiatric disorders: Insomnia.

**DOSE AND ADMINISTRATION**

2.1 General Dosing Information

OFIRMEV may be given as a single or repeated dose.

> Maximum recommended daily dose: 75 mg/kg per day.

2.2 Recommended Dosed: Children

Children 2 to 12 years of age: the recommended dosage of OFIRMEV is 15 mg/kg every 6 hours or 12.5 mg/kg every 8 hours.

**FULL-PREScribing INFORMATION: CONTENTS**

**WARNING: RISK OF MEDICATION ERRORS AND HEPATOTOXICITY**

- When prescribing, preparing, and administering OFIRMEV injection to avoid dosing errors which could result in accidental overdose.

**RISK OF MEDICATION ERRORS AND HEPATOTOXICITY**

- Most of the cases of liver injury are accidental overdose and death. (5.3)
- Do not exceed the maximum recommended daily dose of acetaminophen (by all routes of administration and from all sources) does not exceed maximum daily limits.
- OFIRMEV contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times leading to fatal outcomes. (5.1)
- The risk of liver injury is associated with the use of acetaminophen and is a dose-related effect. (5.1)
- The most common adverse reactions in patients treated with OFIRMEV were nausea, vomiting, headache, and insomnia.

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8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no studies of intravenous acetaminophen in pregnant women; however, epidemiological data on oral acetaminophen use in pregnant women show no increased risk of major congenital malformations. Animal reproduction studies have not been conducted with IV acetaminophen. The results from a large population-based prospective cohort, including data from 26,424 women with live births ascertained through the Medical Birth Registry of Norway, showed no increased risk of major birth defects among children of mothers administered a single intravenous dose of acetaminophen during the first trimester, in contrast to results for oral acetaminophen use (357, 715, and 439). An overall reduction in adverse effects on small-vessel hemostasis. Clinical studies of both

8.2 Labor and Delivery

In a laboratory animal study, repeat doses of acetaminophen were administered to pregnant rats and fetuses. These effects did not occur with doses of 1.2-times the MHDD (based on a body surface area comparison). In contrast, no clastogenicity was noted at a dose of 1500 mg/kg/day via a continuous breeding study. There were no effects on fertility parameters in mice consuming up to 1.7 times the MHDD of acetaminophen, based on a body surface area comparison. The results from a large population-based, case-control study from the National Birth Defects Prevention Study showed that white maternal exposure to acetaminophen during the first trimester had no increased risk of major birth defects among children of mothers administered a single intravenous dose of acetaminophen during the first trimester, in contrast to results for oral acetaminophen use (357, 715, and 439). An overall reduction in adverse effects on small-vessel hemostasis. Clinical studies of both

8.3 Nursing Mothers

The effectiveness of OFIRMEV for the treatment of acute pain and fever in pediatric patients 2 years and older is supported by evidence from adequate and well-controlled studies of OFIRMEV in adults. The safety and effectiveness of OFIRMEV have been shown in infants and children age 2 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Patients with Hepatic Impairment

OFIRMEV is contraindicated in patients with severe hepatic impairment or severe active liver disease and should be used in patients with hepatic insufficiency or hepatic impairment as defined by the Alberta Hepatic Impairment Classification System (AIC). A reduced total daily dose of acetaminophen may be warranted.

8.7 Patients with Renal Impairment

In cases of severe renal impairment (creatinine clearance ≤ 30 mL/min), longer dosing intervals and reduced total daily dose of acetaminophen may be warranted.

10.4 mg dibasic sodium phosphate, USP. pH is adjusted with hydrochloric acid and/or sodium hydroxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The pharmacokinetic exposure of OFIRMEV observed in subjects of similar body weight, gender, and age is similar to that observed in children age 2 years and older.

12.2 Pharmacodynamics

Acetaminophen has been shown to have analgesic and antipyretic actions in animal and human studies. Single doses of OFIRMEV up to 3000 mg and repeated doses of 1000 mg every 6 hours for 48 hours have not been shown to cause a significant effect on platelet aggregation. Acetaminophen does not have any immediate or delayed effects on small-vessel hemostasis. Clinical studies of both

12.3 Pharmacokinetics

Acetaminophen is a non-salicylate antipyretic and non-

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in mice and rats have been completed by the National Toxicology Program to evaluate the carcinogenic potential of acetaminophen. In 2-year feeding studies, F344 rats and B6C3F1 mice were fed a diet containing acetaminophen up to 6600 ppm. Female rats demonstrated equivocal evidence of carcinogenic activity based on increased incidences of mononuclear cell leukemia at 26 times the maximum human daily dose (MHDD) of 4 grams/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.

Mutagenesis

Acetaminophen was not mutagenic in the bacterial reverse mutation assay (Ames test). In contrast, acetaminophen was negative in the various rodent and human somatic chromosomal aberration assay using human lymphocytes. In preclinical Pharmacology (12.3)

Distribution

The pharmacokinetics of OFIRMEV have been studied in patients and healthy subjects from premature neonates up to adults 60 years. The pharmacological profile of OFIRMEV has been generally consistent across all patient groups. Plasma acetaminophen levels were similar in patients of all ages, although treatment in children age 2 years and older is supported by evidence from adequate and well-controlled studies of OFIRMEV in adults. The safety and effectiveness of OFIRMEV have been shown in infants and children age 2 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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