Scientific and Educational Exhibits and Medically Challenging Cases at ANESTHESIOLOGY® 2019

Tara L. Kennedy, M.D., FASA
Chair, *Committee on Scientific and Educational Exhibits*

The ANESTHESIOLOGY 2019 annual meeting in Orlando will feature 20 scientific and educational exhibits. Many of the exhibits will focus on airway management, pain management and peripheral nerve blocks, including use of ultrasound techniques and presentations that educate through the use of computer-based learning, advanced communication technology, handheld devices, videos and simulators. Exhibits portraying practical aspects of patient care such as vascular access, perioperative management issues and echocardiography will also be highlighted this year. Administrative exhibits will provide information on technology and anesthesia. The scientific exhibits will be evaluated by the committee for originality, clinical relevance, scientific merit and visual impact. Judging of the scientific exhibits will occur on Saturday, October 19. Presentation of first-, second- and third-place prizes will take place on Sunday, October 20.

The Medically Challenging Cases continue to grow in popularity, with more than 1,800 submissions this year. The cases will be presented in WA2 at the Orange County Convention Center from Saturday, October 19, through Monday, October 21. The Medically Challenging Cases will all be presented in timed, 10-minute increments in an electronic format without the use of a poster board. Expert facilitators/moderators will promote discussion and interaction between attendees and presenters during each session.

These sessions have served as a venue for the presentation of interesting and challenging cases and allow for one-on-one interaction with presenters and attendees from around the world. They have also served as a springboard for research and clinical protocols that have emanated from the interaction of colleagues and the sharing of information and experiences. Attendees may also view all presented cases on the e-Poster OnDemand system, available throughout the convention center during the conference. Whether you would like additional time to study a specific case, browse through all cases or view a presentation that you missed, the e-Poster OnDemand site will provide attendees with direct access to all cases during – and even after – the conference.

ASA thanks the members of the Committee on Scientific and Educational Exhibits for all their hard work and dedication:

Tara L. Kennedy, M.D., FASA, Chair
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Kristopher M. Schroeder, M.D.

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OFIRMEV® (acetaminophen) Injection—the only IV formulation of acetaminophen in the United States

Take the lead. Appropriate use depends on YOU.

Your patients and institution rely on you to ensure appropriate use of OFIRMEV. Your expertise in anesthesiology means you can lead the way.

- **Be the champion** for appropriate use in your institution
- **Become better informed** to support internal decision processes. That includes meeting the needs of patients who are NPO or intolerant of oral medications, are at-risk for bleeding, or have impaired renal function
- **Engage your colleagues** to build an effective strategy for appropriate use of OFIRMEV in your institution
- **Align with national opioid reduction initiatives**
  - Review your opioid analgesia data annually
  - Share your findings in support of national standards, internal needs, and public reporting

Start now. Help address the needs of your patients and institution by ensuring a balance between cost, availability, and appropriate use of OFIRMEV.

Visit booth #1241 in the exhibit hall at ANESTHESIOLOGY® 201

INDICATIONS AND USAGE

OFIRMEV® (acetaminophen) injection is indicated for the management of mild to moderate pain in adult and pediatric patients 2 years and older, the management of moderate to severe pain with adjunctive opioid analgesics in adult and pediatric patients 2 years and older, and the reduction of fever in adult and pediatric patients.

IMPORTANT SAFETY 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.

CONTRAINDICATIONS

- Acetaminophen is contraindicated in patients with
  - known hypersensitivity to acetaminophen or to any of the excipients in the intravenous 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, 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. Discontinue OFIRMEV immediately at the first sign of skin rash.
- Take care when prescribing, preparing, and administering OFIRMEV Injection to avoid dosing errors, which could result in accidental overdose and death.
- 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. Discontinue OFIRMEV immediately upon occurrence of signs or symptoms associated with allergy or hypersensitivity. Do not use OFIRMEV in patients with acetaminophen allergy.
- The antipyretic effects of OFIRMEV may mask fever.

ADVERSE REACTIONS

- Serious adverse reactions may include hepatic injury, serious skin reactions, allergy, and hypersensitivity.
- The most common adverse reactions in patients treated with OFIRMEV were nausea, vomiting, headache, and insomnia in adult patients and nausea, vomiting, constipation, and pruritus in pediatric patients.

To report SUSPECTED ADVERSE REACTIONS, contact Mallinckrodt Pharmaceuticals at 1-800-778-7898 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see Brief Summary of full Prescribing Information on the adjacent page.

Mallinckrodt Pharmaceuticals

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

BRIEF SUMMARY - Consult full prescribing information before use.

OFIRMEV (acetaminophen) Injection
Initial U.S. Approval: 1951

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 maximum daily limits, and often involve more than one acetaminophen-containing product *[see Warnings and Precautions (5.1)]*.

INDICATIONS AND USAGE

OFIRMEV® (acetaminophen) injection is indicated for
- the management of mild to moderate pain in adult and pediatric patients 2 years and older.
- the management of moderate to severe pain with adjunctive opioid analgesics in adult and pediatric patients 2 years and older.
- reduction of fever in adult and pediatric patients.

CONTRAINDICATIONS

Acetaminophen is contraindicated:
- in patients with known hypersensitivity to acetaminophen or to any of the excipients in the intravenous formulation
- in patients with severe hepatic impairment or severe active liver disease *[see Warnings and Precautions (5.1)]*.

WARNINGS AND PRECAUTIONS

Hepatic Injury

Administration of acetaminophen in doses higher than recommended may result in hepatic injury, including the risk of liver failure and death *[see Overdosage (10)]*. Do not exceed the maximum recommended daily dose of acetaminophen *[see Dosage and Administration (2)]*. The maximum recommended daily dose of acetaminophen includes all routes of acetaminophen administration and all acetaminophen-containing products administered, including combination products.

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) *[see Use in Specific Populations (8.6, 8.7)]*.

Serious Skin Reactions

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. Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Risk of Medication Errors

Take care when prescribing, preparing, and administering OFIRMEV (acetaminophen) Injection in order 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 *[see Dosage and Administration (2)]*.

Allergy and Hypersensitivity

There have been post-marketing reports of hypersensitivity and anaphylaxis associated with the use of acetaminophen. Clinical signs included swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, and pruritus. There were infrequent reports of life-threatening anaphylaxis requiring emergent medical attention. Discontinue OFIRMEV immediately if symptoms associated with allergy or hypersensitivity occur. Do not use OFIRMEV in patients with acetaminophen allergy.

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:
- Hepatic Injury *[see Warnings and Precautions (5.1)]*
- Serious Skin Reactions *[see Warnings and Precautions (5.2)]*
- Allergy and Hypersensitivity *[see Warnings and Precautions (5.4)]*

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in practice.

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 OFIRMEV 1000 mg every 6 hours. A total of 13.1% (n=134) received OFIRMEV 650 mg every 4 hours.

All adverse reactions that occurred in adult patients treated with either OFIRMEV or placebo in repeated dose, placebo-controlled clinical trials at an incidence ≥ 3% and at a greater frequency than placebo are listed in Table 4. The most common adverse events in adult patients treated with OFIRMEV (incidence ≥ 5% and greater than placebo) were nausea, vomiting, headache, and insomnia.

Table 4. Treatment-Emergent Adverse Reactions Occurring in ≥ 3% of OFIRMEV-treated Adult Patients and at a Greater Frequency than Placebo in Placebo-Controlled, Repeated Dose Studies

System Organ Class – Preferred Term	OFIRMEV (N=402) n (%)	Placebo (N=379) n (%)
Gastrointestinal Disorders		
Nausea	138 (34)	119 (31)
Vomiting	62 (15)	42 (11)
General Disorders and Administration Site Conditions		
Pyrexia*	22 (5)	52 (14)
Nervous System Disorders		
Headache	39 (10)	33 (9)
Psychiatric Disorders		
Insomnia	30 (7)	21 (5)

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

Other Adverse Reactions Observed During Clinical Studies of OFIRMEV in Adults

The following additional treatment-emergent adverse reactions were reported by adult subjects treated with OFIRMEV in all clinical trials (n=1020) that occurred with an incidence of at least 1% and at a frequency greater than placebo (n=525).

Blood and lymphatic system disorders: anemia

General disorders and administration site conditions: fatigue, infusion site pain, edema peripheral

Investigations: aspartate aminotransferase increased, breath sounds abnormal

Metabolism and nutrition disorders: hypokalemia

Musculoskeletal and connective tissue disorders: muscle spasms, trismus

Psychiatric disorders: anxiety

Respiratory, thoracic and mediastinal disorders: dyspnea

Vascular disorders: hypertension, hypotension

Pediatric Population

A total of 483 pediatric patients (72 neonates, 167 infants, 171 children, and 73 adolescents) have received OFIRMEV in active-controlled (n=250) and open-label clinical trials (n=225), including 43.9% (n=212) who received 5 or more doses and 31.2% (n=153) who received more than 10 doses. Pediatric patients received OFIRMEV doses up to 15 mg/kg on an every 4 hours, every 6 hours, or every 8 hours schedule. The maximum exposure was 7.7, 6.4, 6.8, and 7.1 days in neonates, infants, children, and adolescents, respectively.

The most common adverse events (incidence ≥ 5%) in pediatric patients treated with OFIRMEV were nausea, vomiting, constipation, and pruritus.

Other Adverse Reactions Observed During Clinical Studies of OFIRMEV in Pediatrics

The following additional treatment-emergent adverse reactions were reported by pediatric subjects treated with OFIRMEV (n=483) that occurred with an incidence of at least 1%.

Blood and lymphatic system disorders: anemia

Gastrointestinal disorders: diarrhea

General disorders and administration site conditions: pyrexia, injection site pain

Metabolism and nutrition disorders: hypokalemia, hypomagnesemia, hypoalbuminemia, hypophosphatemia

Musculoskeletal and connective tissue disorders: muscle spasm

Nervous system disorders: headache

Psychiatric disorders: agitation

Renal and urinary disorders: oliguria

Respiratory, thoracic and mediastinal disorders: atelectasis, pleural effusion, pulmonary edema, stridor, wheezing

Vascular disorders: hypotension, hypertension

DRUG INTERACTIONS

Effects of Other Substances on Acetaminophen

Substances that induce or regulate hepatic cytochrome enzyme CYP2E1 may alter the metabolism of acetaminophen and increase its hepatotoxic potential. The clinical consequences of these effects have not been established. Effects of ethanol are complex, because excessive alcohol usage can induce hepatic cytochromes, but ethanol also acts as a competitive inhibitor of the metabolism of acetaminophen.

Anticoagulants

Chronic oral acetaminophen use at a dose of 4000 mg/day has been shown to cause an increase in international normalized ratio (INR) in some patients who have been stabilized on sodium warfarin as an anticoagulant. As no studies have been performed evaluating the short-term use of OFIRMEV in patients on oral anticoagulants, more frequent assessment of INR may be appropriate in such circumstances.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Published epidemiological studies with oral acetaminophen use during pregnancy have not reported a clear association with acetaminophen use and birth defects, miscarriage, or adverse maternal or fetal outcomes *[see Data]*. Animal reproduction studies have not been conducted with IV acetaminophen. Reproductive and developmental studies in rats and mice from the published literature identified adverse events at clinically relevant doses with acetaminophen. Treatment of pregnant rats with doses of acetaminophen approximately equal to the maximum human daily dose (MHDD) showed evidence of fetotoxicity and increases in bone variations in the fetuses. In another study, necrosis was observed in the liver and kidney of both pregnant rats and fetuses at doses approximately equal to the MHDD. In mice and rats treated with acetaminophen at doses within the clinical dosing range, cumulative adverse effects on reproductive capacity were reported. In mice, a reduction in number of litters of the parental mating pair was observed as well as retarded growth, abnormal sperm in their offspring and reduced birth weight in the next generation. In rats, female fertility was decreased following in utero exposure to acetaminophen *[see Data]*.

The estimated background risk of major birth defects and miscarriages for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Human Data

The results from a large population-based prospective cohort, including data from 26,424 women with live born singletons who were exposed to oral acetaminophen during the first trimester, indicate no increased risk for congenital malformations, compared to a control group of unexposed children. The rate of congenital malformations (4.3%) was similar to the rate in the general population. A population- based, case-control study from the National Birth Defects Prevention Study showed that 11,610 children with prenatal exposure to acetaminophen during the first trimester had no increased risk of major birth defects compared to 4,500 children in the control group. Other epidemiological data showed similar results. However, these studies cannot definitely establish the absence of any risk because of methodological limitations, including recall bias.

Animal Data

Studies in pregnant rats that received oral acetaminophen during organogenesis at doses up to 0.85 times the maximum human daily dose (MHDD = 4 grams/day, based on a body surface area comparison) showed evidence of fetotoxicity (reduced fetal weight and length) and a dose-related increase in bone variations (reduced ossification and rudimentary rib changes). Offspring had no evidence of external, visceral, or skeletal malformations. When pregnant rats received oral acetaminophen throughout gestation at doses of 1.2 times the MHDD (based on a body surface area comparison), areas of necrosis occurred in both the liver and kidney of pregnant rats and fetuses. These effects did not occur in animals that received oral acetaminophen at doses 0.3 times the MHDD, based on a body surface area comparison.

In a continuous breeding study, pregnant mice received 0.25, 0.5, or 1.0% acetaminophen via the diet (357, 715, or 1430 mg/kg/day). These doses are approximately 0.43, 0.87, and 1.7 times the MHDD, respectively, based on a body surface area comparison. A dose related reduction in body weights of fourth and fifth litter offspring of the treated mating pair occurred during lactation and post-weaning at all doses. Animals in the high dose group had a reduced number of litters per mating pair, male offspring with an increased percentage of abnormal sperm, and reduced birth weights in the next generation pups.

Lactation

Risk Summary

There is no information regarding the presence of OFIRMEV in human milk, the effects on the breastfed infant, or the effects on milk production. However, limited published studies report that acetaminophen passes rapidly into human milk with similar levels in the milk and plasma. Average and maximum neonatal doses of 1% and 2%, respectively, of the weight-adjusted maternal dose are reported after a single oral administration of 1 gram APAP. There is one well-documented report of a rash in a breast-fed infant that resolved when the mother stopped acetaminophen use and recurred when she resumed acetaminophen use. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OFIRMEV and any potential adverse effects on the breastfed infant from OFIRMEV or from the underlying maternal condition.

Females and Males of Reproductive Potential

Based on animal data use of acetaminophen may cause reduced fertility in males and females of reproductive potential. It is not known whether these effects on fertility are reversible. Published animal studies reported that oral acetaminophen treatment of male animals at doses that are 1.2 times the MHDD and greater (based on a body surface area comparison) result in decreased testicular weights, reduced spermatogenesis, and reduced fertility. In female animals given the same doses, reduced implantation sites were reported. Additional published animal studies indicate that acetaminophen exposure in utero adversely impacts reproductive capacity of both male and female offspring at clinically relevant exposures *[see Nonclinical Toxicology (13.1)]*.

Pediatric Use

Treatment of Acute Pain

The safety and effectiveness of OFIRMEV for the treatment of acute pain in pediatric patients ages 2 years and older is supported by evidence from adequate and well-controlled studies of OFIRMEV in adults and safety and pharmacokinetic data from adult and 483 pediatric patients across all age groups *[see Dosage and Administration (2.3) and Pharmacokinetics (12.3)]*.

The effectiveness of OFIRMEV for the treatment of acute pain in pediatric patients younger than 2 years of age has not been established.

In patients younger than 2 years, efficacy was not demonstrated in a double-blind, placebo-controlled study of 198 pediatric patients younger than 2 years. Pediatric patients less than 2 years of age, including neonates from 28 to 40 weeks gestational age at birth, were randomized to receive opioid plus acetaminophen or opioid plus placebo. No difference in analgesic effect of intravenous acetaminophen, measured by assessment of reduced need for additional opioid treatment for pain control, was observed.

Treatment of Fever

The safety and effectiveness of OFIRMEV for the treatment of fever in pediatric patients, including premature neonates born at ≥ 32 weeks gestational age is supported by adequate and well-controlled studies of OFIRMEV in adults, clinical studies in 244 pediatric patients 2 years and older, and safety and pharmacokinetic data from 239 patients younger than 2 years including neonates ≥ 32 weeks gestational age.

Geriatric Use

Of the total number of subjects in clinical studies of OFIRMEV, 15% were age 65 and over, while 5% were age 75 and over. 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.

Patients with Hepatic Impairment

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 *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12)]*. A reduced total daily dose of acetaminophen may be warranted.

Patients with Renal Impairment

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

OVERDOSAGE

Signs and Symptoms

In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur. Plasma acetaminophen levels > 300 mcg/mL at 4 hours after oral ingestion were associated with hepatic damage in 90% of patients; minimal hepatic damage is anticipated if plasma levels at 4 hours are < 150 mcg/mL or < 37.5 mcg/mL at 12 hours after ingestion. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Treatment

If an acetaminophen overdose is suspected, obtain a serum acetaminophen assay as soon as possible, but no sooner than 4 hours following oral ingestion. Obtain liver function studies initially and repeat at 24- hour intervals. Administer the antidote N-acetylcysteine (NAC) as early as possible. As a guide to treatment of acute ingestion, the acetaminophen level can be plotted against time since oral ingestion on a nomogram (Rumack-Matthew). The lower toxic line on the nomogram is equivalent to 150 mcg/mL at 4 hours and 37.5 mcg/mL at 12 hours. If serum level is above the lower line, administer the entire course of NAC treatment. Withhold NAC therapy if the acetaminophen level is below the lower line.

For additional information, call a poison control center at 1-800-222-1222.

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