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OFIRMEV: A Recently Introduced Drug

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ALTHOUGH THE CLINICAL use of acetaminophen dates as far back as 1887, it was not until the mid 1950s that it was widely marketed in the United States (Jahr & Lee, 2010). It is recognized as one of the safest and most effective drugs to date and is available in more than 600 pharmaceutical products (Cadence Pharmaceuticals, 2010b). Used as an analgesic and antipyretic, acetaminophen is most commonly available in oral and suppository formulations (Jahr & Lee, 2010). Marketed as the first and only IV form of acetaminophen available in the United States, in January 2011, Cadence Pharmaceuticals launched OFIRMEV. In use in Europe since 2002, the safety and effectiveness of IV acetaminophen are well established. Recognized as "the market leader among all injectable analgesics," Perflagan, OFIRMEV's European counterpart, has become Europe's drug of choice for the management of acute pain in pediatric and adult populations (Cadence Pharmaceuticals, 2010b). Although not formally published, the results of several United States clinical trials support the positive therapeutic effects of IV acetaminophen and mimic the European experience (Jahr & Lee, 2010). Already approved in more than 80 countries, the November 2010 Food and Drug Administration's (FDA's) approval of an intravenous formulation marks the first new class of drugs the United States has seen in two decades (Cadence Pharmaceuticals, 2010a). Now available for use in hospitals across the United States, OFIRMEV has expanded the clinical indications and nursing implications of one of the most widely used drugs in the treatment of acute pain and fever in patients across the lifespan. The purpose of this article is to explore some of the clinical indications and nursing implications for the use of OFIRMEV as a safe and effective analgesic and antipyretic in the perioperative setting.

Clinical Indications

Clinical trials in which 1,020 adults and 355 pediatric patients received IV acetaminophen was the bases on which the FDA approved OFIRMEV's use (Cadence Pharmaceuticals, 2010a). Indicated for the management of mild to moderate pain, severe pain combined with opiates, and the reduction of fevers, clinical trials with OFIRMEV showed remarkable promise for its use in the postoperative setting (Smith, 2011). Historically, the treatment of perioperative pain included nonopioid oral analgesics, IV and oral nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids. Although effective in the treatment of postoperative pain, both NSAIDs and opioids are associated with serious side effects, adverse reactions, and Black Box warnings (Smith, 2011). The anticipated advantage of OFIRMEV is that it can be used alone or in combination with other analgesics, which favors a reduction in patient exposure to serious side effects such as nausea, vomiting, constipation, urinary retention, sedation, and respiratory depression (Vadivelu, Mitra, & Narayan, 2010). The most notable disadvantage of OFIRMEV is its risk of hepatotoxicity. Cadence Pharmaceuticals advises that

A potential reduction in opiate consumption, minimization of adverse events, improvement in pain relief and patient satisfaction are just a few of the anticipated benefits of OFIRMEV.

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caution be used in patients with known or suspected liver disease (Cadence Pharmaceuticals, 2010a).

In a research study conducted by Memis, Inal, Kavalci, Sezer, and Sut (2010), it was concluded that in a multimodal analgesic approach that incorporated the use of IV acetaminophen along with opioids following major surgery, patients experienced decreases in both postoperative pain and sedation scores. In the same study, it was noted that patients reported decreases in nausea and vomiting in the first 24 hours after surgery and that there were significant decreases in the time to extubation (Memis et al., 2010). In a double-blinded placebo-controlled study conducted by Lahtinen et al. (2002), as reported by Memis et al., (2010), "the use of IV acetaminophen reduced the amount opioids used after cardiac surgery" (p. 459). Consistent with the results of previous studies, a double-blinded placebo-controlled multicenter study that was aimed at evaluating the analgesic efficacy and safety of repeated doses of IV acetaminophen concluded that "IV acetaminophen was more effective than the placebo and comparable to nonopioid and opioid analgesics in the management of postoperative pain in a wide range of surgical settings" (Wininger et al., 2010, p. 2364). Duggan and Scott (2009), in a drug profile report published in 2009, reviewed the clinical efficacy and tolerability of IV acetaminophen in adult and pediatric patients with perioperative pain or infection-induced fever. This published report was based on the findings of numerous well-controlled studies and reported that IV acetaminophen was found to be well tolerated by pediatric and adult patients, it provided effective postoperative analgesia, it generally reduced the requirement for opioid rescue medications, and it was rarely associated with significant adverse events (Duggan & Scott, 2009). A literature review of randomized controlled trials of IV acetaminophen for acute pain conducted by Macario and Royal (2010) support the findings of the drug profile report in that of the 16 studies reviewed, and they each suggested that the use of IV acetaminophen is both safe and effective in the management of acute pain in pediatric and adult populations.

According to Cadence Pharmaceuticals (2011b), "the effectiveness of OFIRMEV for the treatment of acute pain and fever has not been studied in pediatric patients less than two years old but in children two years of age and older it is the only IV drug approved to treat both pain and fever" (para. 4). According to recent studies conducted in Europe, IV acetaminophen is being used more often in neonates, and dosing guidelines have been published by two European Centers (Anderson & Allegaert, 2009). The current use of IV acetaminophen in neonates and infants up to 12 months of age in the UK, Ireland, and Great Britain is not known; however, a recent online survey of Linkmen of the Association of Pediatric Anesthetists was taken, and 54% of those who responded indicated the use of IV acetaminophen in infants younger than 1 year (Wilson-Smith & Morton, 2009). Although considered an off-label use in many countries, the use of IV acetaminophen in children less than 2 years of age is common, and the rationale for its use is guided by the pharmacokinetics and dynamics of the drug. Two Cadence Pharmaceutical-sponsored clinical trials have been completed in the United States (Maxwell, n.d.). One 48-hour study of pediatric inpatients was aimed at determining the pharmacokinetics and safety in acute pain and fever, whereas the other study's aim was to look at the safety and efficacy of IV acetaminophen in pediatric patients. Both studies were designed to assess the safety of repeated doses in pediatric patients from full-term neonates to adolescents. Study findings revealed that pharmacokinetic parameters were similar to those previously determined after oral and rectal administration with clearance reduced in neonates and young infants, reaching adult levels at approximately 2 years of age. The analgesic effects were correlated to plasma concentrations, and IV acetaminophen may be a safe postoperative analgesic for neonates and children, if dosing guidelines are followed (Maxwell, n.d.).

Effective treatment of postoperative pain is extremely important in neonates, children, and adults. With significant correlations to clinical outcomes, the effective treatment of postoperative pain is paramount. Current research suggests that as part of a multimodal approach to perioperative pain, "the use of IV acetaminophen can reduce opiate consumption, minimize adverse events, improve pain relief and patient satisfaction, facilitate earlier recovery, and reduce costs of hospitalization" (Wininger et al., 2010, p. 2349). Clinically indicated for the use of acute pain and fevers, OFIRMEV's efficacy to safety profile mimics that of acetaminophen and offers new options in a multimodal approach to acute and postoperative pain management (Anderson & Allegaret, 2009; Moller et al., 2005).

Drug History

According to Maxwell (n.d.), "Efforts had been made for many years to develop an intravenous formulation of acetaminophen" (History, para. 1). PROPACETAMOL a prodrug of Perflagan that required reconstitution before administration was once available, but due to infusion-site reactions, adverse effects, reconstitution errors, and insolubility concerns, its use was discontinued prompting the need for a well-tolerated IV formulation (Cadence Pharmaceuticals, 2010; Duggan & Scott, 2009). Cadence Pharmaceuticals (2010b) "believes that OFIRMEV is the only stable, pharmaceutically acceptable intravenous formulation of acetaminophen" (para. 3). Adequate pain control is a major area of concern in the United States and is the focus of much research (Vaddivelu, Mitra, & Narayan, 2010). Cadence Pharmaceuticals expects that OFIRMEV will open the doors for a new therapeutic approach for treating pain and fevers in the hospital setting (Cadence Pharmaceuticals, 2010a).

Pharmacodynamics/Pharmacokinetics

After more than a hundred years of study, acetaminophen's exact mechanisms of action remain elusive. It is believed that its action is associated with the centrally acting cyclooxygenase inhibition and may explain the antipyretic effects (Jahr & Lee, 2010). According to Duggan and Scott (2009), "acetaminophen has been shown to act at both the central and peripheral components of the pain pathway and that the analgesic effects may also involve the serotonergic system" (p. 102). The IV route of administration gives 100% bioavailability, and with an onset of 5 minutes, OFIRMEV has been shown to achieve a greater maximum concentration than the rectal and oral formulations (Jahr & Lee, 2010; Wilson-Smith & Morton, 2009). The therapeutic effects of IV acetaminophen can be seen within 1 hour of administration with a duration of approximately 4 to 6 hours ("Intravenous Paracetamol," 2009). OFIRMEV exposes the liver to less acetaminophen because it is distributed in systemic circulation before being metabolized in the liver, essentially bypassing the first pass effect. Bypassing the first pass effect increases the safety profile of OFIRMEV, resulting in a reduced risk of liver toxicity. OFIRMEV is mainly excreted in the urine with an elimination half-life that is approximately 2 to 4 hours in children, adolescents, and adults (Jahr & Lee, 2010).

Nursing Implications

The administration of medications is an important part of the care that patients receive in the hospital setting and is the chief responsibility of the nurse. The nurse is often the first person to recognize, assess, and intervene when pain control is needed. IV administration is the most effective and convenient route and is often the most feasible (Edmunds & Mayhew, 2009). With ease of administration and rapid onset, the IV route often provides a more predictable and reliable therapeutic effect (Candiotti et al., 2010). With an onset occurring within 30 minutes, IV acetaminophens antipyretic effects are superior to other routes of administration and may be the only available route during the perioperative period (Duggan & Scott, 2009). The study conducted by Macario and Royal (2010) suggest that rapid onset of IV acetaminophen compared with oral or rectal administration is preferred when treating acute surgical pain especially when oral intake is not appropriate.

Packaged as a single dose vial with a concentration of 1,000 mg/100 ml, OFIRMEV requires no reconstitution and offers a simple dose calculation increasing its ease of administration (Cadence Pharmaceuticals, 2011a). With the safety and efficacy that mimics oral and rectal routes of administration, OFIRMEV requires minimal to no increase in patient monitoring (Moller et al., 2005). In the treatment of acute pain and fevers, OFIRMEV can be administered with little disturbance to patient activity or rest. Jahr and Lee (2010) suggest that effective pain control provides more than just immediate clinical benefits, but it also increases patient satisfaction. Lacking the sedative effects seen with the administration of opioids, OFIRMEV can be used as an effective premedication likely increasing the patient's compliance, response, and benefits of postoperative therapies, such as incentive spirometry use and ambulation. The availability of OFIRMEV can virtually erase the physical challenges that often arise when administering oral or rectal medications in the pediatric population.

Recommended Dosage

With the addition of an IV formulation, acetaminophen holds the distinction of being the only nonopioid analgesic available in oral, rectal, and IV formulations (Duggan & Scott, 2009). Used in more than 80 countries since its approval in 2001, the safety and effectiveness of IV acetaminophen have been demonstrated (Jahr & Lee, 2010). Emerging as an asset in the management of pain and fevers, the introduction of OFIRMEV has expanded the use of one of the safest drugs available. "Clinicians will now be better able to use a multi-modal approach to pain management in the hospital setting" (Cadence Pharmaceuticals, 2010, para. 4). Despite the abundance of evidence related to the benefits of appropriate postoperative pain control, postoperative pain management remains unsatisfactory (Vaddivelu et al., 2010). For the successful management of acute pain and fevers, advances must continue to be made in the development of safe and effective drugs. "As the first new class of IV pain medication the United States has seen in two decades", OFIRMEV is an example of the successful advances research has made in this area (Cadence Pharmaceuticals, 2011b, para. 2). A potential reduction in opiate consumption, minimization of adverse events, improvement in pain relief and patient satisfaction, facilitation of an earlier recovery, and reduction in the costs of hospitalization are all anticipated benefits of OFIRMEV, supporting its "ability to fill an important unmet medical need in the United States" (Candiotti et al., 2010, p. 1842; Wininger et al., 2010; see Table 1 for general dosing information.).

Appendix

Table 1 General Dosing Information

Age Group	Dose Given Every 4 Hours	Dose Given Every 6 Hours	Maximum Single Dose	Maximum Total Daily Dose of Acetaminophen (By Any Route)
Adults and adolescents (13 years and older) weighing ≥50 kg	650 mg	1,000 mg	1,000 mg	4000 mg in 24 hours
Adults and adolescents (13 years and older) weighing <50 kg	12.5 mg/kg	15 mg/kg	15 mg/kg (up to 750 mg)	75 mg/kg in 24 hours (up to 3,750 mg)

Note: OFIRMEV may be given as a single or repeated dose for the treatment of acute pain or fever. No dose adjustment is required when converting between oral acetaminophen and OFIRMEV dosing in adults and adolescents. The maximum daily dose of acetaminophen is based on all routes of administration (i.e., intravenous, oral, and rectal) and all products containing acetaminophen.
Recommended dosage: adults and adolescents.
Adults and adolescents weighing 50 kg and greater: The recommended dosage of OFIRMEV is 1,000 mg every 6 hours or 650 mg every 4 hours, with a maximum single dose of OFIRMEV of 1,000 mg, a minimum dosing interval of 4 hours, and a maximum daily dose of acetaminophen of 4,000 mg per day.
Adults and adolescents weighing less than 50 kg: The recommended dosage of OFIRMEV is 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours, with a maximum single dose of OFIRMEV of 15 mg/kg, a minimum dosing interval of 4 hours, and a maximum daily dose of acetaminophen of 75 mg/kg per day.

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