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Acetaminophen by Infusion

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Acetaminophen is a nonsteroidal, nonsalicylate analgesic and antipyretic that is, today, the most common medication ingredient found in oral and rectal over-the-counter and prescription drugs. However, it was not until 2010 that Ofirmev (acetaminophen), an injection form of acetaminophen, was approved for treating mild to moderate pain, as an adjunct to opioids for severe pain, and reduction of fever in those younger than 2 years. Thus, intravenous acetaminophen may be appropriately used in a wide variety of settings and nurses who are knowledgeable and informed about the correct use of intravenous acetaminophen will be able to reduce the potential for medication misadventures. In this article, the uses and cautions for Ofirmev are discussed.

Although the analgesic and antipyretic properties of acetaminophen (*N*-acetyl-*p*-aminophenol, known as paracetamol in other nations) have been known for over a century, it was not until the mid-20th century that acetaminophen really came into widespread use. Today, the safety profile and effectiveness of acetaminophen have made it one of the leading agents for relief of fever and reduction of mild to moderate pain for both adults and children (Bertolini et al., 2006; Cranswick & Coghlan, 2000).

For several decades both oral and rectal forms have been available in a myriad of over-the-counter (OTC) products and combination products of acetaminophen and selected narcotics are available by prescription. However, it was not until 2010 that an intravenous (IV) form of acetaminophen was approved by the Federal Food and Drug Administration (FDA) for use in the United States (FDA, 2010).

The approved indications for use of acetaminophen by injection include (1) management of mild to moderate pain, (2) use as an adjunct with opioid analgesics in severe pain, and (3) reduction of fever in adults and children older than 2 years. Thus IV acetaminophen may be appropriately used in a wide variety of settings, and nurses who are knowledgeable and informed about the correct use of IV acetaminophen will be able to reduce the potential for medication misadventures.

In the following discussion, an overview of selected uses and benefits of IV acetaminophen therapy is discussed. Administration guidelines, necessary cautions, and implications for nursing are also addressed.

Looking for Safety

Even though the analgesic and antipyretic properties of acetaminophen were actually known as long ago as the 1880s, synthesis and marketing for medicinal use was not heavily pursued until middle of the 20th century. In the early 20th century, phenacetin was very popular as a sole agent or in combination with other substances for relief of pain and fever (e.g., APC [aspirin, phenacetin, codeine]). And when phenacetin use decreased because of evidence of renal toxicity or carcinogenicity, aspirin (salicylic acid) again became the primary drug for fever and mild pain relief in both adults and children. But, aspirin also had associated toxicities and researchers, determined to find a nonaspirin agent, turned their attention back to acetaminophen, which appeared to have a safer profile. But, this safer profile for acetaminophen did not spur an immediate flood of acetaminophen products and aspirin continued to be the primary choice for fever and pain relief.

By the early 1950s however, when association between aspirin and Reye's syndrome in children with viral infections was identified, it became imperative to develop a nonaspirin antipyretic for children. By 1955, McNeil Pharmaceuticals introduced acetaminophen as Tylenol Elixir the first aspirin-free prescription pain and fever reliever approved by the FDA for children. Less than 5 years later (in 1959) additional Tylenol formulations products were approved for OTC use for both children and adults, and by 1976 Tylenol was the leading OTC analgesic drug in the United States (Tylenol, 2014).

The "age of acetaminophen" had begun and in the next few decades a proliferation of acetaminophen products came on the market from many pharmaceutical companies. Some contained acetaminophen as the main medicinal ingredient and others were combinations of acetaminophen and another medication. Most were OTC formulations of different strengths and different combinations; others, primarily combinations of acetaminophen and an opioid, were available only by prescription. By the 1990s acetaminophen was the most common medicinal ingredient used in the United States. Today acetaminophen is found in a myriad of agents marketed for fever reduction and pain relief, but also as sleeping aides, allergy relief, and cough or cold remedies. For a list of selected examples of common medicines containing acetaminophen, see Table 1.

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Table 1. Examples of Medicines With Acetaminophen as an Ingredient

OTC Products Containing Acetaminophen	
Acephen (suppositories)	Mapap[a]
Actifed[a]	Midol[a]
Alka-Seltzer[a]	Nortemp Children's Suspension
Anacin[a]	Nyquil[a]
Benadryl[a]	Q-Pap[a]
Contac[a]	Robitussin[a]
Coricidin[a]	Silapap[a]
DayQuil[a]	Sudafed[a]
Dimetapp[a]	Theraflu[a]
Dristan[a]	Triaminic[a]
Exedrin[a]	Tylenol[a]
FeverAll (suppositories)	Vanquish[a]
Genapap	Vick's 44[a]

Prescription Drugs Containing Acetaminophen
Percocet, Roxicet, Endocet, Tylox (oxycodone and acetaminophen)
Vicodin, Lorcet, Lortab, Norco (hydrocodone and acetaminophen)
Tylenol w/codeine, Floricet w/codeine (codeine and acetaminophen)
Floricet, Dolgic Plus, Zebutal (butalbital, caffeine, and acetaminophen)
Ultracet (tramadol and acetaminophen)

Notes. OTC = over the counter.
[a]There are a variety of acetaminophen-containing products under this brand name.
Data from: Cadence Pharmaceuticals, Inc. (2013c); Know Your Dose (2014).

In fact, there are so more than 600 acetaminophen-containing products on the market, used for so many purposes, that the both the public and professionals are strongly cautioned to take all sources of acetaminophen into consideration in order not to exceed the daily dose recommendations of 4 g per day. While generally safe, acetaminophen is conjugated by a limited number of liver enzymes, and exceeding daily dose recommendations (or when used in the presence of severe active liver impairment) overwhelms these enzymes and there is a distinct potential for serious hepatotoxicity (Acetaminophen Awareness Coalition, 2011; FDA, 2011).

Beyond Oral or Rectal–Acetaminophen for Injection

After decades of evidence related to the safety profile and effectiveness of acetaminophen (when used as directed), there was increased interest in developing an IV formulation. However, developing a stable, safe, and acceptable formulation took time. So it was 2002 before an IV acetaminophen formulation was finally available in most European countries (Harrington, 2013). A decade later, Ofirmev (acetaminophen for injection) manufactured by Cadence Pharmaceuticals (Now Mallinckrodt Pharmaceuticals) was approved for use in the United States (FDA, 2010). Today, although IV acetaminophen is still fairly new in the United States, it is being used in a wide variety of settings as monotherapy or as part of a multimodal form of pain management in many different settings (Harrington, 2013; Passero & Stannard, 2012; Sinatra et al., 2012).

Table 2. Ofirmev (Acetaminophen Injection)

Description: Nonsalicylate antipyretic and nonopioid analgesic agent.

Use: (1) the management of mild to moderate pain,

(2) as an adjunct with opioid analgesic drugs for moderate to severe pain and

(3) to reduce fever in adults and children (>2 years of age).

How supplied: 100-mL glass vial containing 1 g of acetaminophen (10 mg/mL)

Mechanism of action: Acts on the hypothalamus to reduce fever, analgesic effect not known.

Contraindication: Severe active liver disease, allergy to acetaminophen

Warnings/precautions: Hepatotoxicity in doses greater than total daily dose recommendations; rare serious skin reactions (Stevens–Johnson syndrome or toxic epidermal macrolysis); allergy or hypersensitivity to acetaminophen.

Black box warning: Dose in milligrams (mg), and not milliliters (mL). Dosing in individuals weighing <50 kg must be based on body weight. Use properly programmed infusion pump, and maximum daily dose of acetaminophen must not exceed maximum daily limits.

Onset of action: Analgesia: 5–10 minutes; antipyretic: within 30 minutes

Duration of action: Analgesia 4–6 hours, antipyretic >6 hours

Dosing. ≥12 year and ≥50 kg: 650 mg q 4h or 1000 mg q 6 hours (maximum single dose 1000 mg, maximum daily dose 4 g daily),

Dosing. 2 to 12 years: 12.5 mg/kg q 4h or 15 mg q 6h (maximum single dose 15 mg/kg) (750 mg), maximum daily dose, 75 mg/kg/day (<3.75 g daily).

Administration: Administer from vial by inserting a vented IV set through the septum of the vial—undiluted over 15 minutes.

Doses smaller than 1000 mg should be withdrawn from vial, placed in a syringe and infused over 15 minutes via syringe pump. Once opened vial should be used within 6 hours.

Transition Administration IV ≥ Oral: No adjustment in dose is necessary

Adverse reactions: Nausea or vomiting, headache, insomnia, pyrexia

Drug/drug interactions: Should not be infused with other medications.

Note. Data from Lexi Comp (2014); Cadence Pharmaceuticals. Inc. (2013b).

In Table 2, some of the pertinent information about Ofirmev is outlined. Benefits, cautions, and examples of use in different patient situations are discussed and suggestions for patient education are identified.

Many benefits of IV acetaminophen relate specifically to the route of administration–IV administration as opposed to oral or rectal. For instance, there are many situations where oral or rectal administration is not an option, such as endotracheal intubation, impaired or inactive gastrointestinal mobility, nausea and/or vomiting, type of surgery or injury, level of sedation,

and so forth. Another benefit of IV administration is that it leads to almost immediate bioavailability and thus, more rapid clinical analgesia than oral or rectal forms and it allows for more evenly maintained levels over repeated doses (Bertolini et al., 2006). In addition, with IV administration peak levels can be reached at lower concentrations that are less hepatotoxic than equivalent oral doses (Jahr & Lee, 2010). This is a major benefit since one of the major cautions with acetaminophen is hepatotoxicity related to high concentrations.

Another important benefit of IV acetaminophen is that it is approved for treating both pain and fever in children older than 2 years. This is important since there is no other IV product approved for both pain and fever in pediatric patients (Cadence Pharmaceuticals, 2013a; 2013b; 2013c).

When used in a multimodal approach with opioids for acute postoperative pain (including abdominal, pelvic, or orthopaedic surgeries), IV acetaminophen has been shown to reduce the amount of opioid needed, extend the time between opioid doses (rescue doses), and reduce the adverse reactions to opioid analgesics (Gonzalez & Ramamoorthy, A., 2014; Harrington, 2013; Macario & Royal, 2011; Passero & Stannard, 2012). Reducing the amount of opiates necessary for adequate pain control reduces the potential for negative effects of opiates such as constipation, respiratory depression, and sedation. Including IV acetaminophen as part of multimodal perisurgical or postsurgical analgesia has also been shown to reduce the incidence of adverse gastrointestinal effects such as nausea and vomiting as well as reducing the potential for gastric irritation associated with some other agents (Apfel et al., 2014. Maintaining adequate pain control and reducing potential for opioid complications can play a major role in early ambulation and shorter lengths of stay.

Intravenous acetaminophen has also been shown to be effective as monotherapy in minor surgery, ambulatory surgery, and the emergency department. In a study of emergency department patients with acute leg pain, 1000 mg of IV acetaminophen was found to be as effective as 10 mg of morphine (Craig, Jeavons, Probert, & Benger, 2012).

Cautions

While there is a significant body of literature about the efficacy and safety of IV acetaminophen, there are also cautions that must be considered (see Table 2). One of the major cautions is dosing. Exceeding the daily dose recommendations for acetaminophen increases the potential for hepatotoxicity and, therefore, the total daily dose of all acetaminophen products must be considered: oral, rectal, and IV. Other cautions and contradictions include the possibility of serious skin reactions (although this is extremely rare).

Nursing Implications and Conclusion

Acetaminophen (paracetamol) is a nonsalicylate, nonopioid analgesic, and antipyretic that has a high safety profile when used as directed to relieve mild or moderate pain or to relieve fever in both children and adults. While oral and rectal formulations of acetaminophen have been used successfully and with relative safety for over half a century, it has only been in the past decade that an IV formulation of acetaminophen was available. The IV formulation of acetaminophen allows for use when oral or rectal administration is not an option for moderate pain, as an adjunct to opioids in more severe pain and as an antipyretic for adults and children older than 2 years. And, even though the IV use of acetaminophen is more recent, its efficacy and safety in many settings are well documented. Thus, nurses in a variety of practice arenas may be administering IV acetaminophen.

Nurses, knowledgeable about acetaminophen use and aware of safe use precautions, can be a first-line defense against potential medication misadventures or untoward patient experiences with IV acetaminophen. Safe administration, monitoring for efficacy, and identifying any possible adverse reactions are, of course, vital nursing responsibilities for IV use of acetaminophen (or any other medication). Patient education is also an important nursing function with all medications. However, with IV acetaminophen, nurses also have the opportunity to educate patients about the safe use of all forms of acetaminophen. Instructing patients that even after discharge they need to be aware of the multiple sources of acetaminophen (prescription and nonprescription) when they calculate their daily dose and referring them to such sources of information as "Know Your Dose" will provide a safety feature that extends beyond the immediate health situation.

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