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Intravenous Acetaminophen Use in Infants and Children

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Acetaminophen has been a cornerstone of the management of mild to moderate pain and the treatment of fever for more than 50 years.[1] The availability of only oral and rectal dosage formulations in the United States, however, has limited its use in the hospital setting. An intravenous (IV) preparation would allow for rapid, reliable drug delivery to patients in the immediate post-operative setting or in cases where enteral administration is not possible due to underlying disease. On November 2, 2010, the Food and Drug Administration approved the first injectable acetaminophen product for use in adults and children 2 years of age and older.[2,3] This issue of *Pediatric Pharmacotherapy* will review this new product and highlight studies of IV acetaminophen use in infants and children.

Mechanism of Action

The exact mechanism by which acetaminophen produces its analgesic and antipyretic effects remains undefined. The primary mechanism of action is believed to be inhibition of cyclooxygenase (COX), with a predominant effect on COX-2. Inhibition of COX enzymes prevents the metabolism of arachidonic acid to prostaglandin H_2, an unstable intermediate byproduct which is converted to pro-inflammatory compounds. In the central nervous system, inhibition of COX enzymes reduces concentrations of prostaglandin E_2, which lowers the hypothalamic set-point to reduce fever, and activation of descending inhibitory serotonergic pathways to produce analgesia.[1-4]

While acetaminophen shares the analgesic and antipyretic properties of other COX inhibitors such as aspirin and the non-steroidal anti-inflammatory drugs (NSAIDs), it does not possess significant anti-inflammatory properties. Unlike aspirin, acetaminophen does not inhibit thromboxane and, as a result, does not alter platelet aggregation.[1-4]

Recent studies have suggested that acetaminophen may work through additional mechanisms, including modulation of the body's endogenous cannabinoid system. One of the metabolites of acetaminophen (N-arachidonoylphenolamine or AM404) inhibits the uptake of anandamide, increasing concentrations of endogenous cannabinoids. These substances can both modulate serotonergic descending pain pathways and lower body temperature. Other investigators have suggested that acetaminophen produces direct inhibition of N-methyl-D-aspartate (NMDA) receptors, blocking substance P-dependent synthesis of nitric oxide through the L-arginine-nitric oxide pathway and reducing nociception. These proposed mechanisms are not likely exclusive; in fact, they may all be components of an interwoven series of responses to acetaminophen administration.[1-4]

Pharmacokinetics and Pharmacodynamics

The pharmacokinetic/pharmacodynamic profile of IV acetaminophen has been extensively studied in the pediatric population. Overall, the results are similar to data gathered in adults. In recent premarketing studies, the maximum serum concentration achieved after IV acetaminophen administration was up to 70% higher than that achieved from the same dose given orally. The overall exposure as measured by the area under the concentration time curve (AUC), however, was similar. Maximum serum concentrations have ranged from a low of 25 $\pm$ 4 mcg/mL in neonates to a high of 31 $\pm$ 9 mcg/mL in adolescents.[2,3]

Acetaminophen is widely distributed throughout the body, penetrating most tissues except fat. Average values for the volume of distribution in pharmacokinetic studies conducted by the manufacturer were 1.1 L/kg for neonates, infants, and adolescents, 1.2 L/kg in children, and 0.8 L/kg in adults. Acetaminophen is only weakly bound to serum proteins (10-25%).[2,3] It readily penetrates into the cerebrospinal fluid (CSF). In a study of 32 children undergoing surgery, a single IV dose of acetaminophen 15 mg/kg produced CSF concentrations ranging from 1.3 to 18 mg/L, with CSF to plasma ratios ranging from 0.06 to 2.0.[5] The average time to peak CSF concentration was 57 minutes.

Hepatic metabolism is the primary mechanism for acetaminophen elimination. There are three major metabolic pathways: glucuronide conjugation (accounting for 40-60% of a dose in adults), sulfate conjugation (20-40%), and N-hydroxylation via the cytochrome P450 isozyme CYP2E1 (< 15%). The latter mechanism results in a highly reactive intermediate metabolite, N-acetyl-*p*-benzoquinone imine (NAPQI), which undergoes further conjugation with glutathione to form nontoxic thiol metabolites. Excessive doses of acetaminophen can result in depletion of glutathione stores, producing accumulation of NAPQI and hepatotoxicity. Due to differences in the rate of development of metabolic enzymes, neonates, infants, and children produce a larger percentage of sulfate conjugates and a smaller percentage of glucuronide conjugates than adults. Immaturity of CYP2E1 in young children also results in less production of NAPQI, explaining in part their decreased likelihood for acetaminophen-induced hepatotoxicity.[1-3]

The half-life of acetaminophen varies by age. In pharmacokinetic trials conducted by the manufacturer of the IV preparation, neonates had the longest half-life, with an average of 7.0 $\pm$ 2.7 hrs. Infants had a shorter half-life of 4.2 $\pm$ 2.9 hrs. Older children, adolescents, and adults had similar values (3.0 $\pm$ 1.5 hrs, 2.9 $\pm$ 0.7 hrs, and 2.4 $\pm$ 0.6 hrs, respectively). Based on the pharmacokinetic differences observed in neonates and infants compared to older children and adults, the manufacturer suggests that the IV acetaminophen dose for neonates should be approximately 50% of the pediatric dose. The recommended dose for infants between 1 month and 2 years of age should be 33% of the pediatric dose. In both neonates and infants, a 6-hour dosing interval is recommended.[2,3]

Additional pharmacokinetic studies conducted in neonates have produced similar results. The longer elimination half-life observed in neonates is most pronounced in those born prematurely.[6,7] In 2008, Palmer and colleagues found that acetaminophen clearance rates increased with increasing postmenstrual age.[7] The authors treated 50 neonates with IV acetaminophen. Patients were dosed according to postmenstrual age: 28-32 weeks, 10 mg/kg; 32-36 weeks, 12.5 mg/kg; and $\geq$ 36 weeks, 15 mg/kg. Clearance rates ranged from 4.4 L/hr/70kg at 34 weeks to 6.3 L/hr/70 kg at 46 weeks.

The onset of analgesia typically occurs within 5 to 10 minutes after administration of IV acetaminophen. Peak effects occur at approximately 1 hour, with a 4-6 hour duration of effect. Fever reduction is generally seen within 30 minutes of acetaminophen administration.[2,3]

Clinical Trials

Although only recently introduced in the United States, IV acetaminophen has been approved for use in more than 80 countries since its release in 2001. Prior to that time, IV propacetamol, a prodrug of acetaminophen, had been used for more than a dozen years in Europe. Several studies have been published demonstrating the efficacy of propacetamol in the management of pain and fever in children. The newer IV acetaminophen product, however, has largely replaced propacetamol because of its ease of use and fewer infusion-site reactions.[1,8]

In clinical practice, IV acetaminophen has typically been used as part of a multimodal analgesic regimen. Administration in the immediate post-operative setting may attenuate the onset of acute pain while the patient is recovering from general anesthesia and potentially reduce subsequent analgesic use.[1] The analgesic efficacy of IV acetaminophen has been studied in infants and children undergoing a variety of dental and surgical procedures. Alhashemi and Daghistani conducted two randomized controlled trials comparing 15 mg/kg IV acetaminophen to 1 mg/kg meperidine in children undergoing surgery.[9,10] In their 2006 study, both drugs proved effective in 80 children who underwent tonsillectomy.[9] Average pain scores on admission to the recovery room were similar, 3.1 with acetaminophen and 2.1 with meperidine ($p = 0.147$). Nurse satisfaction scores were also equivalent between the groups. Children in the acetaminophen group were less sedated, however, and had a significantly shorter time to discharge from the recovery room (15 vs. 25 min, $p = 0.05$).

In their 2007 study, Alhashimi and Daghistani found that IV acetaminophen produced less initial pain relief than meperidine in 40 children undergoing dental surgery (mean objective pain score 3 in the acetaminophen group and 2 in the meperidine group, $p = 0.012$).[10] As in their previous study, Ramsey sedation scores were significantly higher in the meperidine group (4 vs. 2 in the acetaminophen group, $p = 0.013$). After 20 minutes, there were no differences in pain or sedation scores between the groups.

Murat and colleagues randomized 183 children less than 12 years of age to receive a single dose of either IV acetaminophen (15 mg/kg) or propacetamol (30 mg/kg) after inguinal hernia repair.[11] Efficacy was assessed from the end of the 15 minute infusion to 6 hours. Both drugs produced a rapid reduction in pain scores, with effects lasting for more than 4 hours in most children. Only 20% of children in each group required an additional analgesic. Injection site pain occurred in only 15% of the IV

acetaminophen group, compared to 33% of the propacetamol group ($p = 0.005$).

In 2008, Capici and colleagues compared the efficacy of IV and rectal acetaminophen in 50 children between 2 and 5 years of age undergoing adenotonsillectomy.[12] The children were randomized to receive either 15 mg/kg IV acetaminophen or 40 mg/kg rectal acetaminophen. All received 2 mcg/kg fentanyl. Forty-six children completed the study, with 45 requiring rescue analgesia. Although both groups had similar pain scores, the time to first rescue dose was longer in the children receiving rectal acetaminophen than in those given an IV dose (10 hrs vs. 7 hrs, $p = 0.01$).

Hong and colleagues published two studies of IV acetaminophen last year.[13,14] In a study published in *Anesthesiology*, 63 children (6-24 months of age) who were to receive fentanyl as parent/nurse-controlled analgesia after undergoing ureteroneocystostomy were randomized to receive acetaminophen mixed with the fentanyl or fentanyl alone.[13] While postoperative pain scores were similar between the children receiving the drug combination and those given fentanyl alone, the total fentanyl dose was significantly lower in the acetaminophen-fentanyl group (8.3 ± 3.7 vs. 18.1 ± 4.6 mcg/kg/day on postoperative day 1, $p = 0.021$ and 7.0 ± 2.4 vs. 16.6 ± 5.5 on day 2, $p = 0.011$).

These investigators also demonstrated IV acetaminophen's opioid-sparing effects in a prospective, randomized, double-blind study of 55 children undergoing inguinal hernia repair. The authors found that the combination of IV acetaminophen (20 mg/kg) and ketorolac (1 mg/kg) administered after induction of general anesthesia provided significantly better pain control than placebo and reduced overall postoperative fentanyl use (0.5 mcg/kg vs. 1.37 mcg/kg in the controls). The placebo group had higher rates of sedation and vomiting, likely associated with more frequent use of fentanyl.[14]

Antipyretic efficacy was assessed in a randomized double-blind study of 67 children (1 month-12 years of age) who received a single IV dose of either 15 mg/kg acetaminophen or 30 mg/kg propacetamol.[15] Prior to dosing, the patients' rectal body temperatures ranged from 38.5-41° C. Control of fever (a temperature $\leq$ 38° C) occurred in 79% of the children given acetaminophen and 75% of those given propacetamol. The only significant difference between the groups was the higher incidence of infusion-site reactions with propacetamol (28.1% compared to 5.7% with acetaminophen, $p = 0.0134$).

Premarketing Studies in the United States

A total of 355 infants and children took part in premarketing clinical trials for IV acetaminophen, including two active-controlled trials and three open-label trials. The patients enrolled in trials of IV acetaminophen safety ranged in age from premature neonates ($\geq$ 32 weeks gestation) to adolescents. Only children 2 years of age and older were enrolled in efficacy studies conducted by the manufacturer.[2] None of these trials have yet been published in the medical literature.

Contraindications and Precautions

Intravenous acetaminophen is contraindicated in patients with severe hepatic impairment or patients with a known hypersensitivity to acetaminophen or its excipients (mannitol, cysteine hydrochloride, dibasic sodium phosphate, hydrochloric acid, or sodium hydroxide). It should be used with caution in patients with active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia, or severe renal impairment.[2,3]

Adverse Effects

During premarketing clinical trials, the most common adverse effects observed in infants and children given IV acetaminophen were nausea, vomiting, constipation, pruritus, agitation, and atelectasis (all reported in 5% of patients or more). Other reactions reported in at least 1% of children included: anemia, tachycardia, abdominal pain, diarrhea, injection site pain, edema, hypoalbuminemia, hypokalemia, hypomagnesemia, hypophosphatemia, hypervolemia, muscle spasm, headache, insomnia, oliguria, pulmonary edema, pleural effusion, stridor, wheezing, rash, hypotension, or hypertension.[2,3]

Hepatotoxicity, although rare with standard dosing, remains a concern with the use of acetaminophen in infants and children. The use of the IV product does not appear to increase the risk for hepatotoxicity compared to oral or rectal administration. In a 2008 retrospective study by Allegaert and colleagues, serum transaminase values were examined in 189 neonates before, during, and after IV acetaminophen administration.[16] The regimen consisted of a 20 mg/kg loading dose followed by doses of 10 mg/kg given up to every 6 hours in patients with a gestational age > 36 weeks, every 8 hours in patients born at 31-36 weeks, or every 12 hours in those born prior to 31 weeks gestation. The patients ranged in age from 1-182 days (average 5 days), with an average gestational age of 38 weeks. The average length of therapy was 60 hours (range 6-480 hours), with nine doses given per patient (range 2-80 doses). There were no significant differences in alanine transaminase or gamma-glutamyl transferase when pretreatment

values were compared with values during or immediately after treatment. Aspartate aminotransferase values declined (r = -0.24, 95% CI -0.34 to -0.12). Subgroup analysis of the premature neonates produced similar results.

Drug Interactions

Chronic oral acetaminophen has been shown to increase INR values in patients taking warfarin. Although this interaction has not been studied in patients receiving IV acetaminophen, INR values should be closely monitored when it is used in patients receiving warfarin. Administration of probenecid reduces acetaminophen clearance and increases the risk for toxicity.

Availability and Dosing Recommendations

Acetaminophen injection (Ofirmev™; Cadence Pharmaceuticals) is available in a 1,000 mg/10 mL (10 mg/mL) single-use vial. The cost per vial is currently $10.18. Acetaminophen injection does not require further dilution prior to administration. No dose adjustment is needed when converting between oral and IV acetaminophen. For adults and adolescents weighing 50 kg or more, the manufacturer recommends a dose of 650 mg IV every 4 hours or 1,000 mg IV every 6 hours, with a maximum dose of 4,000 mg per 24 hours. For adults and adolescents weighing less than 50 kg and children 2-12 years of age, a weight-based strategy is recommended: 12.5 mg/kg IV every 4 hours or 15 mg/kg IV every 6 hours, with a maximum dose of 75 mg/kg every 24 hours. All doses should be given over 15 minutes using a syringe pump.[2,3]

Summary

The availability of an IV formulation of acetaminophen provides a means of administration to patients unable to tolerate oral or rectal administration. In clinical trials, IV acetaminophen has been shown to provide relief for mild to moderate pain in infants and children, reduce opioid requirements following surgery, and reduce fever. While the cost of this new product will likely preclude routine use, it may be a useful adjunct or alternative analgesic/antipyretic in select cases. Continued assessment of its use will be necessary to determine the role of IV acetaminophen in routine pediatric practice.

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Formulary Update

The following actions were taken on the Inpatient Formulary at the March Pharmacy and Therapeutics Committee meeting:

1. Nifedipine extended release (Procardia XL®) was added to the Formulary.
2. Omega-3 acid ethyl esters (Lovaza®) was added for patients with dyslipidemias.
3. Clomiphene (Clomid®) was removed from the Formulary for inpatient use.
4. Updates to the High Alert Medication list, IV Administration Guidelines: Adult Acute Care, Look-Alike/Sound-Alike list, and Hazardous Drug list were also approved.

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