Intravenous Acetaminophen: An Alternative to Opioids for Pain Management?

You are consulted to co-manage a 7-month-old girl after surgical reduction of intussusception. The surgery was uncomplicated, and the patient was extubated in the operating room. Pain management will consist of intravenous (IV) opioids, specifically morphine. IV acetaminophen has recently become available at your institution, and you wonder if it could reduce the need for morphine in this patient. Would this then minimize the potential for adverse effects?

IV acetaminophen, under the brand name Ofirmev®, was approved in 2010 by the US Food and Drug Administration for the management of mild to moderate pain, the management of moderate to severe pain with adjunctive opioid analgesics, and the reduction of fever in patients aged ≥2 years at a dosage of 15 mg/kg every 6 hours to a maximum of 75 mg/kg per day.1 The cost for a single-use vial is about $10. Although there are 10 years of worldwide experience, the use of IV acetaminophen in North America has remained limited despite growing evidence supporting its benefits and relative safety. Use in infants has been particularly limited due to its off-label status.

In the double-blind, randomized controlled trial recently published in JAMA,2 Ceelie et al investigated the utility of IV acetaminophen in infants. More specifically, they sought to determine whether the routine use of IV acetaminophen would reduce postoperative morphine requirements in patients aged <1 year undergoing major thoracic (noncardiac) or abdominal surgery.

Between 2008 and 2010, investigators recruited infants with a postconceptual age of ≥36 1/7 weeks to 1 year of age weighing >1500 g who were planning to undergo major thoracic (noncardiac) or abdominal surgery at the Erasmus MC–Sophia Children’s Hospital in the Netherlands. Severely ill children, defined as those on extracorporeal membrane oxygenation, with neurologic or hepatic dysfunction or renal insufficiency, were excluded, as were children who had received prenatal or postnatal opioids or psychotropic drugs for >24 hours, those with known intolerance or allergy to either acetaminophen or morphine, and those who had received opioids in the 24 hours preceding surgery. Of the 139 eligible patients, 74 were randomized to receive either acetaminophen or morphine postoperatively, and 71 ultimately participated in the study. Health care providers and families were blinded to group allocation. All patients received standardized intraoperative anesthesia and a loading dose of morphine 30 minutes before the anticipated end of the procedure. The study drug, acetaminophen or morphine, was begun within 5 minutes of arrival in the ICU. Acetaminophen was administered as an intermittent IV infusion at a dosage of 30 mg/kg per day in 4 doses whereas morphine was...
administered as a continuous infusion. All patients received IV normal saline as a placebo in the frequency in which the other group was receiving their drug. Morphine was given as a rescue medication to patients in either group when pain scores on validated scales, obtained routinely and when behavior suggested pain, demonstrated ongoing pain and distress.

The patient population in this study is one that would generally be cared for in an ICU, with 45.5% of patients in the acetaminophen group and 36.8% in the morphine group having received postoperative ventilation. The range of duration of postoperative ventilation was −15 to 45 hours in both groups.

The primary outcome was the cumulative morphine dose, including the 100-μg/kg intraoperative loading dose, which was significantly lower in the acetaminophen group with a median of 121 μg/kg per 48 hours [interquartile range: 99–264] compared with the morphine group with a median of 357 μg/kg per 48 hours [interquartile range: 220–605] (P < .001). This finding represents a 66% (95% confidence interval [CI]: 34 to 109) reduction in cumulative morphine dosage. This reduction was more profound in patients ≥11 days of age compared with patients ≤10 days of age, with cumulative morphine doses in the acetaminophen group 73% (95% CI: 30 to 114) lower and 49% (95% CI: −6 to 89) lower than in the morphine group in their respective age groups. Interestingly, the total morphine rescue dose, the number of morphine rescue doses, and the number of patients requiring rescue doses did not differ significantly between the 2 groups. In addition, the median pain scores were similar in both groups. This finding suggests that morphine as dosed in this study and IV acetaminophen are equally efficacious in providing baseline analgesia.

A reduction in morphine dosage is desirable as a means of minimizing drug-related adverse effects. However, although some studies have shown a decrease in morphine dosage with the introduction of IV acetaminophen, no published study has demonstrated a significant decrease in morphine-related adverse effects with the use of IV acetaminophen. Although this finding can be attributed to the fact that adverse effects are relatively rare events, which studies are often not powered sufficiently to detect, stronger evidence that IV acetaminophen is an overall safer drug and therefore directly capable of improving outcomes is still needed. The general safety of appropriately dosed IV acetaminophen in pediatric patients is accepted; however, it should be recognized that safety in the neonatal age group is largely assumed from the safety of rectal administration of acetaminophen. Additional safety parameters in neonates are projected from the relative immaturity of the cytochrome P450 enzymes and higher glutathione stores. It must be noted that concerns regarding accidental overdose in neonates persist, and education of health care providers is required. Physicians should therefore still be cautious in using IV acetaminophen in children younger than the age limit of 2 years approved by the US Food and Drug Administration.

Overall, this study provides promising evidence that in infants and neonates who have undergone major noncardiac surgery, IV acetaminophen provides analgesia similar to morphine in the initial 48-hour postoperative period. Although this population is specific, and more acutely ill than typical pediatric patients because they required some ongoing respiratory support, it is reasonable to suppose that IV acetaminophen would be equally as effective in more stable patients. It remains to be proven in the literature, in pediatric patients with mild to moderate pain but who are unable to take acetaminophen via other routes of administration, if IV acetaminophen may go beyond the reduction of the need for morphine and eliminate this need altogether if the overall pain control requirements are less.

Although it is not an ideal, large, multi-institutional study involving a wide cross-section of the hospitalized pediatric population, this well-designed study contributes to the already existing body of literature that supports the use of IV acetaminophen in pediatric patients. As such, you cautiously prescribe IV acetaminophen in your 7-month-old patient as a key component of her postoperative pain control while ensuring that ongoing monitoring of her pain is in place.

REFERENCES


3. Hong JY, Kim WO, Koo BN, Cho JS, Suk EH, Kil HK. Fentanyl-sparing effect of acetaminophen as a mixture of fentanyl in intravenous parent-/nurse-controlled


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