Pain Panacea for Opiophobia in Infants?

Kanwaljeet J. S. Anand, MBBS, DPhil, FRCPCH

Intravenous acetaminophen (paracetamol) is suggested for use as an opioid-sparing analgesic for children requiring surgery or emergency care, despite limited data on its efficacy and toxicity in infants and children. In this issue of JAMA, the randomized trial by Ceelie and colleagues addresses this evidence gap by showing clinically significant reductions in morphine use among neonates or infants receiving postoperative analgesia. Among patients randomized to receive acetaminophen (n=33) or morphine (n=38) postoperatively, the cumulative morphine dose during the first 48 hours following surgery was 121 µg/kg (interquartile range, 99-264) vs 357 µg/kg (interquartile range, 220-605), respectively—a 66% relative reduction between groups (P<.001). There were no differences in the number of patients requiring morphine rescue doses or in pain scores.

These findings merit consideration because of the careful study design, well-matched study groups, and the magnitude of effects observed. However, in addition to the limitations of small sample size, single-center study site, and lack of safety data, these findings also should be interpreted in light of several other considerations.

First, given the brief duration of exposure to morphine (48-72 hours) in the trial, it is unlikely that patients in the morphine group developed opioid tolerance, although opioid-induced hyperalgesia could have increased their analgesic requirements. Careful clinical evaluations can differentiate opioid-induced hyperalgesia from opioid tolerance, although standardized clinical tests or biomarkers for opioid-induced hyperalgesia are currently unavailable for this age group. It is possible that some patients in the morphine group may have developed opioid-induced hyperalgesia, partly explaining the wide range of morphine requirements in this group. Another possibility is the accumulation of morphine-3-glucuronide, a metabolic product formed preferentially in infants and associated with behavioral excitability and hyperalgesia. These effects were less likely in the group receiving intravenous acetaminophen, perhaps accounting for some of its opioid-sparing effects.

Second, synergism between morphine and acetaminophen cannot be ruled out, because all patients received morphine (100 µg/kg) before leaving the operating room. The mechanism(s) of acetaminophen analgesia are currently unclear, but several mechanisms could potentiate opioid analgesia. Oral acetaminophen preparations are frequently combined with opioids. However, a randomized trial studying the interactions between intravenous morphine and acetaminophen in 90 adult postoperative patients found additive but not synergistic effects (clinicaltrials.gov Identifier: NCT1366313). In the study by Ceelie et al, some findings suggest that acetaminophen may have been more effective in older infants. In stratified analysis, the cumulative morphine dose in the acetaminophen group compared with the morphine group was 49% lower among neonates aged 0 through 10 days (median dose, 111 µg/kg per 48 hours vs 218 µg/kg per 48 hours, respectively) and was 73% lower among infants aged 11 through 365 days (median dose, 152 µg/kg per 48 hours vs 553 µg/kg per 48 hours). For a study designed to investigate the efficacy of acetaminophen, it is arguable that collapsing the age-related strata should have been based on the pharmacokinetics of acetaminophen rather than morphine. Nevertheless, reporting data on morphine dose reductions according to the age-group strata originally designed in this study will be of interest for clinicians.

Third, although the age distribution of opioid-related adverse effects in this study population was not reported, an age-related susceptibility to opioid adverse effects is well known with regard to respiratory depression and possibly hypotension. The study by Ceelie et al was designed to focus on the adverse effects of opioids, whereas the toxicity or possible adverse effects of acetaminophen were not evaluated. Hepatic toxicity following intravenous acetaminophen is not uncommon and has been reported following 10-fold dosing errors in infants but also can occur after therapeutic oral doses. Other possible adverse effects include systemic anaphylaxis or localized effects and pain at the site of injection (in one study, this occurred in 15% of patients receiving acetaminophen and in 33% of those receiving propacetamol). However, given the dose and time of exposure in this study, those adverse effects would be unlikely.

See also p 149.
Fourth, infants are potentially less susceptible to hepatic toxicity from oral or rectal acetaminophen because of the delayed maturation of cytochrome P450 enzymes and relatively higher glutathione stores. One major concern is that prescribing long-term, standard doses every 6 hours—particularly for younger children or those with critical illness or poor enteral nutrition—may lead to toxicity. Future studies should not only monitor renal function and liver function but also should measure acetaminophen-protein adducts in all children, particularly neonates, receiving intravenous acetaminophen. Developmental expression and polymorphisms of cytochrome P450 enzymes (CYP2E1, 1A2, 3A4) on acetaminophen-induced hepatotoxicity or of N-deacetylase and N-acetyltransferase enzymes on the potential for nephrotoxicity should also be investigated.

Is opiophobia in infants an outmoded fallacy, or is there still a clinical bias against the use of opioids in infants and children? Previous studies reveal a widespread reluctance to treat pain with adequately dosed opioids, particularly in nonventilated infants. Wide variability in clinical practices continues at present, mostly driven by personal preferences or institutional practices, with up to 100-fold differences in initial opioid doses, average daily doses, cumulative doses, or peak infusion rates. Based on morphine pharmacokinetics in this age group, Ceelie et al followed a strict analgesic protocol for both groups of infants. This reduced clinical variability but also reduced their morphine infusion rates (averaging 2.5 μg/kg per hour in the acetaminophen group and 7.4 μg/kg per hour in the morphine group for the first 48 hours), thus minimizing the opioid-related adverse effects they observed. These doses are significantly lower than those generally prescribed for postoperative infants.

Titrating morphine analgesia carefully (based on pain scores) is more labor intensive than the common practice of slightly oversedating infants who require opioid analgesia for painful conditions, such as following operations. However, this approach may avoid the respiratory depression, hypotension, and opioid tolerance observed in many centers. Busy clinical units will have to choose between the nursing resources required to follow such a labor-intensive protocol or to tolerate a relatively low incidence of oversedation and opioid-related adverse effects. Theoretically elegant approaches have little value in clinical practice if they are not practically feasible in the clinical settings for which they were designed. However, research studies such as the report by Ceelie et al are invaluable because they bring methodological rigor and continue to set new standards for future clinical practice.

Conflict of Interest Disclosures: The author has completed and submitted the ICME Form for Disclosure of Potential Conflicts of Interest and none were reported.

Additional Contributions: I would like to thank Laura P. James, MD (University of Arkansas for Medical Sciences), and Russell W. Chesney, MD, Samir H. Shah, MD, MBA, FRCP, and Andreas Schingshackl, MD, PhD (University of Tennessee Health Science Center), for critically reviewing this article.

REFERENCES