Codeine Use in Pediatric Patients

Codeine is a weak opioid that is used to treat mild to moderate pain in both children and adults. Recently, the WRHA Child Health Pharmacotherapy Subcommittee recommended removing codeine and codeine-containing products from the hospital formulary following increasing safety concerns regarding the use of codeine, particularly in children. At this point, removal of codeine from pediatric patient care areas is voluntary, as the committee needs to work with various stakeholders prior to any formal implementation.

The Issue

Codeine requires metabolism by the CYP2D6 liver enzyme into its active form, morphine, in order to provide analgesia. CYP2D6 displays significant genetic polymorphism; up to 10% of the population are poor metabolizers of codeine, while ultra-rapid metabolizers occur in 0.5 to 1% of Chinese, Japanese and Hispanic patients, 1 to 10% of Caucasian patients, 3% of African American patients, and 16 to 28% of North African, Ethiopian, and Arab patients.\(^{(1)}\)

A “normal” metabolizer converts approximately 10% of a dose of codeine into active morphine. Poor metabolizers will create little, if any, morphine and thus will experience minimal analgesia. Rapid or ultra-rapid metabolizers can produce 50 – 75% more morphine than a “normal” metabolizer, which can lead to significant side effects, including respiratory depression and death.\(^{(2-5)}\) These effects are related to both dose and duration of codeine use.

The same effect is seen in mothers who breastfeed their infants; in nursing mothers who are ultra-rapid metabolizers, morphine levels are much higher in breast milk, which has lead to apneas and death in newborns.\(^{(6)}\)

Genetic polymorphism is unpredictable and therefore it is very difficult to know how patients will respond to codeine.

The Literature

More Codeine Fatalities After Tonsillectomy in North American Children – Kelly et al, Pediatrics 2012 (3)

- Three case reports of North American children (2 in Canada) who were prescribed age/weight appropriate doses of codeine post-op tonsillectomy.
- Two children died and one required resuscitation, mechanical ventilation and naloxone.

Is maternal opioid use hazardous to breast-fed infants? – Hendrickson and McKeown, Clinical Toxicology 2012(6)

- 6 case reports involving breastfeeding mothers who used codeine and their infants
- Infants experienced apneas, bradycardia, sedation and death.

Health Canada also published an advisory statement in 2008 which warns health care providers and the public about the risks of codeine use in breastfeeding mothers.\(^{(1)}\) More recently, Health Canada released a recommendation that codeine and codeine-containing products should not be used in children less than 12 years of age.\(^{(7)}\)
Therapeutic Alternatives

Given the variable metabolism and subsequent safety concerns with codeine, the following oral analgesics are recommended for pediatric patients:

1) For mild to moderate pain:
   a. Acetaminophen 10 – 15 mg/kg/dose PO q4-6h PRN (do not exceed 5 doses/day; adult maximum dose 4 g/day)
   b. Ibuprofen 4 – 10 mg/kg/dose PO q6-8h PRN (max: 40 mg/kg/day; adult maximum dose 3.2 g/day)

2) For moderate to severe pain:
   a. Morphine (immediate release) 0.1-0.2 mg/kg/dose PO q4-6h PRN (can increase to a maximum of 0.5 mg/kg/dose; usual maximum adult dose for opioid naive patients 30 mg q4h)
   b. Hydromorphone (immediate release) 0.03-0.08 mg/kg/dose every 3-4 hours as needed (up to 2 mg/dose for opioid naïve patients).

Scheduled analgesia as opposed to “as needed” analgesia is suggested to control pain as recommended by the World Health Organization. (8)

Common Misconceptions

1) Morphine is more dangerous than codeine.
   a. False. Morphine is a much more predictable and reliable analgesic without genetic variability in its metabolism. Codeine metabolism is varied and hence a less safe alternative.

2) Codeine has fewer side effects than morphine.
   a. False. Codeine has the same side effect profile as all opioid analgesics.(9) Poor metabolizers are at an increased disadvantage; they experience the same side effects without the analgesia.

3) Morphine is too hard to prescribe and too hard for families to acquire in the community.
   a. False. Morphine is a common narcotic and is available in numerous dosage forms (multiple tablet strengths, as well as 2 commercially available oral solutions). Community pharmacists are able to assist patients with any questions or concerns they have regarding the use of this medication.

References


