Pain management in children: Part 2 — A transition from codeine to morphine for moderate to severe pain in children

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Introduction

Opioids remain the agent of choice for the treatment of moderate to severe pain in both adults and children. Codeine, an opioid analogue, is commonly used in the treatment of mild to moderate pain in both adults and children. However, there has been growing concern about the safety of codeine use in children. This second part of the article on pain management in children will focus on codeine's questionable efficacy and safety concerns about the use of codeine in children.

Codeine

Codeine has gained much popularity as a single agent or in combination with a non-opioid agent, such as acetaminophen, for the treatment of mild to moderate pain in children. Based on the authors' experiences, the widespread use of codeine for different types of pediatric pain is partially due to the perception that weak opioids such as codeine have a low incidence of adverse effects compared to "stronger" opioids such as morphine. There is little evidence, however, to support the commonly held view of a lower incidence of serious side effects with codeine. It may be true that a single dose of 1 mg/kg of codeine given to neonates presents a small risk of respiratory depression;¹ however, with repeated doses of codeine, significant respiratory depression has been reported in neonates.¹⁻³

Codeine's questionable efficacy

Several studies including children have shown that codeine is no more effective at providing pain control than an NSAID or another opioid such as oxycodone. Clark et al.⁴ compared reduction in pain

scores 60 minutes after a single dose of ibuprofen (10 mg/kg), acetaminophen (15 mg/kg) or codeine (1 mg/kg) in more than 300 children with musculoskeletal trauma.⁴ The group found that 50% of children in the ibuprofen group achieved adequate analgesia, and this was more than codeine (40%) or acetaminophen (36%).⁴ In another study, Charney et al.⁵ randomized 177 children with suspected orthopedic injury to receive either codeine (2 mg/kg) or oxycodone (0.2 mg/kg). Although both groups had significant reductions in pain scores measured every 30 minutes for 3 hours, children who received oxycodone had statistically significant greater reduction in pain scores compared with codeine at all time intervals.⁵

Codeine metabolism and genetic polymorphism of CYP2D6

Since codeine has a very low affinity for opioid receptors, its analgesic effect is dependent on its conversion to morphine through the cytochrome P-450 enzyme 2D6 (CYP2D6).⁶ CYP2D6 catalyzes the conversion of codeine into morphine. Morphine is then conjugated with glucuronic acid by glucuronidases to form 2 main morphine metabolites, the inactive morphine-3-glucuronide (M3G) and the active morphine-6-glucuronide (M6G).⁶ Genetic polymorphism of CYP2D6 is well known and characterized in the literature.⁷ A person with 2 nonfunctional alleles of CYP2D6 is considered to have poor drug metabolism, whereas a person with 1 or 2 functional alleles is considered to have extensive metabolism, and one who has duplicated or amplified active CYP2D6 genes is considered to have ultra-rapid metabolism.⁸ The incidence

of poor and ultra-rapid metabolizers has been reported to vary from 0–10% and 0–29%, respectively, among various populations.⁹ The incidence of genetic polymorphism of CYP2D6 in children is not known, but it is assumed to be similar to what is reported in adults.

It has been well defined in both the medical literature and from clinical experience that there is variability in inter-individual response to codeine.¹⁰ The analgesic effect of codeine is dependent on its conversion by CYP2D6 to the active morphine M6G metabolite. Since the gene that encodes the CYP2D6 enzyme is highly polymorphic, there is variation in the metabolic efficiency of codeine among different ethnic groups. About 10% of the Caucasian population and 30% of the Chinese population have poor CYP2D6 drug metabolism, making codeine an ineffective analgesic agent.^{1,10,11} Therefore, the analgesic efficacy of codeine has been questioned both in adults and children.¹² Although hydromorphone and oxycodone also undergo metabolism by the CYP2D6 enzyme, unlike codeine, the parent compounds are also active opioids.¹³ Therefore, the pain relief provided by hydromorphone and oxycodone is not dependent on metabolism by CYP2D6. This suggests that hydromorphone and oxycodone are possible options for children known to have a poor metabolizer phenotype or children for whom genotype is unknown.¹³ Genotyping of the CYP2D6 enzyme is not routinely done in the clinical setting, as it is expensive and not widely available outside of research facilities.¹⁴

Safety concerns with codeine in ultra-rapid metabolizers

There is also growing concern about the safety of codeine. Due to the genetic polymorphism of CYP2D6, individuals with amplified activity of CYP2D6 enzymes can metabolize codeine to morphine much faster, resulting in higher than expected morphine blood levels.¹⁴ The prevalence of ultra-rapid metabolizers is estimated to be 1% in those of Chinese, Japanese and Hispanic descent, 3% in African Americans and 1%–10% in Caucasians. The highest prevalence occurs in 16%–28% in the North African, Ethiopian and Arab populations.¹⁴ It is difficult to predict who will be an ultra-rapid codeine metabolizer based solely on the metabolizer status within different ethnic groups. Genetic tests are available on the market, but are not widely accessible outside of the research setting.¹⁴

There have been several cases reported in the literature describing morphine intoxication in

children after ingesting codeine. Madadi et al.¹⁵ reported a case of a breastfed male infant who died after his mother took Tylenol #3 for postpartum pain.^{15,16} Postmortem toxicology testing of the infant revealed the infant had a blood concentration of morphine of 70 ng/mL¹⁵ (neonates receiving morphine for analgesia have a usual morphine serum range of 10 to 12 ng/mL¹⁷). The analysis of the expressed breast milk from the mother revealed a morphine concentration of 87 ng/mL. A genotype analysis of the mother found that she was heterozygous for CYP2D6*2A allele and a CYP2D6*2x2 gene duplication, making her an ultra-rapid metabolizer of codeine.¹⁵ It was therefore postulated that since the mother was a rapid metabolizer of codeine, higher than expected morphine levels crossed into the breast milk, resulting in morphine intoxication in the breastfed infant.¹⁵ In 2008, Health Canada issued a warning to nursing mothers about the rare but serious health risk to breastfed babies posed by codeine use while breastfeeding.¹⁴

In another case, a healthy 2-year-old boy died of morphine intoxication after taking codeine after an elective adenotonsillectomy procedure.¹⁸ The child was sent home with a prescription for codeine and acetaminophen syrup every 4 to 6 hours as needed for postoperative pain. Shortly after going home, the child was found to have no vital signs and resuscitation efforts failed. Postmortem examination revealed that the child had evidence of bronchopneumonia, a codeine blood concentration of 0.70 mg/L and morphine level of 32 ng/mL; there were no other drugs or metabolites found in the blood.¹⁸ The child's morphine blood levels exceeded therapeutic levels and may have contributed to respiratory depression and death. A genotype analysis of the child revealed that he was an ultra-rapid metabolizer of codeine.¹⁸ Despite a codeine dose within the recommended range, ultra-rapid metabolism of codeine can lead to a toxic accumulation of morphine. The boy had other contributing factors, such as bronchopneumonia and sleep apnea, that may have played a role in his death. Bronchopneumonia and sleep apnea may have increased his risk of hypoxemia, leading to alterations in mu-opioid receptors and increased sensitivity to morphine.¹⁸

Since the fatal case described above of a toddler who had received codeine after adenotonsillectomy, there have been 3 additional fatal or life-threatening cases reported from North America. The first case described a 4-year-old (27.6 kg) First Nations' boy who underwent adenotonsillectomy for obstructive sleep apnea syndrome (OSAS) and

recurrent tonsillitis.¹⁹ He was discharged from a regional hospital in northern Ontario, Canada, on liquid codeine at an age-appropriate dose of 8 mg/dose, up to 5 doses a day as needed. His parents reported him to be sedated and lethargic the day after hospital discharge. The next afternoon, after a total of 4 doses of codeine, he was brought to the hospital without vital signs. His postmortem morphine level was 17.6 ng/mL (therapeutic morphine range is 4.5 ± 2.1 ng/mL).^{19,20} His toxicology screen revealed a blood codeine level to be in the expected range after therapeutic use, and no other medications were detected. The child's genotyping revealed a gene duplication and a CYP2D6 ultra-rapid metabolizer phenotype.¹⁹

In the second case, a 3-year-old girl (14.4 kg) of Middle Eastern descent underwent tonsillectomy for OSAS and was discharged home on a combination of codeine and acetaminophen (15 mg codeine/150 mg acetaminophen) after a 24-hour stay at a Canadian children's hospital.¹⁹ More than 6 hours after her final codeine dose (total 60 mg of codeine), she was found unresponsive, with a fever of 100°F with minimal respiration and an oxygen saturation of 65%. Her blood morphine concentration was 17 ng/mL. After successful resuscitation, mechanical ventilation and naloxone dosing (1.5 mg), she showed prompt improvement in her symptoms. Her genotype was revealed to be CYP2D6 extensive metabolizer.

In the third case, a 5-year-old boy (29 kg) from the southern United States underwent bilateral myringotomy tube placement and adenotonsillectomy for recurrent tonsillitis and snoring.¹⁹ After surgery, he was prescribed acetaminophen and codeine (12 mg codeine) every 4 hours (within the recommended range of 6 mg/kg/day). Twenty-four hours after his discharge, his mother found the child without vital signs. The child's postmortem codeine blood concentration was 79 ng/mL and morphine blood concentration was 30 ng/mL. The measured codeine concentration of 79 ng/mL approximately 8 hours after his last dose was at the 56th percentile of predicted pediatric codeine concentrations. The measured morphine concentration of 30 ng/mL was at the 99th percentile of predicted concentrations at the normal pediatric rate of conversion. Although genotyping was not done in this child, it is highly suspected that he was a CYP2D6 ultra-rapid metabolizer, given the exceedingly high morphine concentration relative to codeine.¹⁹

In the cases described above, the children were given age- and weight-appropriate doses of codeine. Their genotype of being extensive or

ultra-rapid CYP2D6 metabolizer of codeine put them at higher risk of morphine intoxication.

Morphine as an alternative to codeine

Morphine remains the most commonly used opioid in children with severe pain, because it has demonstrated efficacy and relative safety when used appropriately in pain management in both adults and children.^{21,22} In a systematic review of morphine treatment in children with postoperative pain, it was shown that parenteral morphine was more effective than placebo in lowering the pain score, achieving longer time to first analgesic request and lowering consumption of rescue analgesics when compared to placebo.²³ When compared to other analgesic agents, morphine had similar efficacy to fentanyl, bupivacaine or ketorolac, in the outcome measures mentioned above.²³ Oral morphine is considered to have equal if not greater efficacy in providing pain relief when compared to codeine, as codeine is a prodrug and its analgesic effect is dependent on its conversion to morphine.

The safety of morphine use in children has been of primary concern for many parents and health care providers because it is perceived to have more associated risks (such as more side effects) and potential for misuse. Morphine has a similar side effect profile to most opioids, such as hydromorphone and oxycodone. The most frequently reported side effects for morphine are vomiting, sedation, pruritus and urinary retention.^{23,24} Among the side effects caused by opioids, respiratory depression is of greatest concern, especially in young infants.²⁴ There is no indication that given equianalgesic doses, morphine causes more side effects than the other opioids.²⁴ Lynn et al.²⁵ found that neonates, infants and children are most susceptible to respiratory depression following intravenous administration of morphine if the morphine blood concentration was higher than 20 ng/mL.^{25,26} Respiration has been found to be depressed several hours after morphine administration, and the onset might not occur until hours after administration.^{27,28} Although severe respiratory depression needing treatment is rare, it can be catastrophic; it is therefore very important to monitor the child's respiration following administration of morphine.²⁴

Another common misconception is that children can become addicted to morphine more easily than adults. Similar to adults, psychological dependence or addiction to opioids is rare when they are used appropriately in children for the treatment of pain.²⁹ Due to the long-time popu-

larity of codeine being prescribed for the treatment of postoperative pain in both adults and children, many community pharmacists are unfamiliar with the use of morphine in children and may have misconceptions about its use. Some pharmacists may believe that morphine use is not safe in children. In actuality, morphine can be used safely in children of all ages, including neonates.^{24,29,30}

Clinical recommendations

Due to concerns about the lack of efficacy and safety of codeine, The Hospital for Sick Children (SickKids) has removed codeine and all codeine-containing products from the hospital formulary. With the removal of codeine from the formulary, suitable alternatives for the treatment of moderate to severe pain are needed. For moderate pain, it is recommended to start the dose of oral morphine at the lower recommended dose range (i.e., in SickKids' *Drug Handbook and Formulary* 2011/2012, the recommended dose range for oral morphine is 0.2–0.5 mg/kg/dose, so one would start at 0.2 mg/kg/dose). By replacing codeine with morphine, our organization is hoping to achieve maximum efficacy in relieving pain and to increase the safety of opioid use in everyone, regardless of their CYP2D6 genotype.

Morphine is an appropriate alternative to codeine, as it is available in a variety of dosage forms for easy administration in children. Morphine is available as an oral liquid, short-acting and long-acting capsules and tablets in multiple strengths to allow flexible dosing regimens. For easy conversion, an equipotent dose of morphine is approximately one-tenth the dose of codeine. Besides morphine, there are several other oral opioids that can be used in place of codeine. Their efficacy and safety are similar to codeine as long as an equipotent dose is used. See Table 1.

Although combination products such as Tylenol #1, 2 or 3 are popular agents used to manage pain in adults and older children, they offer limited utility for dose escalation in titrating the opioid dose according to the patient's response. Most

combination products have a non-opioid component such as acetaminophen with a maximum daily dose, which can limit the upward titration of the opioid dose.²⁹ If parents do not understand that combination products contain 2 active ingredients such as codeine and acetaminophen, they may give their child additional acetaminophen without realizing that it is already contained in the combination product. This can lead to overdosing of acetaminophen in the child. For these reasons combination products are not usually recommended for the treatment of pain in children.

It is important to remember that analgesic dosing for infants and children is calculated based on the child's weight, and to consult a pediatric dosing reference to ensure appropriate dosing of morphine. Examples of pediatric dosing references are SickKids' *Drug Handbook and Formulary* and the Lexi-Comp *Pediatric and Neonatal Dosage Handbook*.²⁹ The goal is to control pain as rapidly and safely as possible, and thus, the starting dose should be at the lower end of the recommended dose range and titrated according to the patient's response. Administration of multiple, small, ineffective doses of analgesic may result in prolonged pain, exacerbation of anxiety and even severe adverse effects of the analgesic, such as respiratory depression.³² Pharmacists should be able to anticipate common adverse effects associated with opioid use, such as nausea, vomiting, constipation and pruritus, and recommend preventative strategies to minimize distress and to ensure that adequate pain management is not compromised. Most opioid side effects can be easily prevented or treated with simple interventions such as laxatives to prevent constipation, and anti-emetics and anti-pruritics for nausea and/or vomiting.²⁹

Conclusion

In summary, choosing the appropriate pharmacotherapy is key in providing adequate pain control in children. The analgesic agent has to be effective and safe to use. Due to the recent safety concerns with codeine, SickKids recommends oral morphine as the agent of choice for the treatment of moderate to severe pain, and has developed a knowledge translation strategy (Appendix 1, available at www.cpjournal.ca) to support this practice change. ■

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TABLE 1 Opioid equianalgesic conversion chart³¹

Drug	Equipotent PO dose
Codeine	200 mg
Morphine	Acute: 60 mg Chronic: 30 mg
Hydromorphone	Acute: 6–7.5 mg Chronic: 4–6 mg
Oxycodone	20–30 mg

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