Summary Statement on the Restriction of Codeine

Issue

- In November 2012, the Drugs and Therapeutics Committee (DTC) approved a restriction on codeine and all codeine-containing products on AHS Provincial Drug Formulary, restricting use of these products to patients 18 years of age and older.

Key Message

Codeine must be metabolized to its active metabolite morphine to produce a therapeutic effect. Due to genetic polymorphism a significant percentage of the population are either poor metabolizers or ultra-rapid metabolizers of codeine. As a result, they experience very poor analgesic effects (poor metabolizers) or are at risk of very serious adverse effects (ultra-rapid metabolizers).

Impetus for Change

- Multiple case reports of unexpected toxicity and death in ultra-rapid metabolizers[1]
- Ultra-rapid metabolizers can comprise up to 10-30% of some ethnic populations[1,2]
- Morphine provides a more predictable analgesic response than codeine.

Implications for Practice

- Scheduled use of NSAIDs (e.g. ibuprofen) and/or acetaminophen is recommended to manage moderate to severe pain if no contraindications exist
- Use additional physical (ice/heat) and psychological (distraction/relaxation) techniques to manage pain when appropriate
- Children with moderate to severe pain requiring an opioid should be prescribed oral morphine rather than codeine. Doses may be given as required ("prn") when pain is not adequately managed with acetaminophen and/or NSAIDs alone. Morphine provides a more predictable response than codeine.

Recommendation

Morphine is the preferred alternative to codeine in pediatrics for moderate to severe pain

For infants greater than 6 months of age, children and adolescents:

*Initial **oral** dose in opioid naïve:* Morphine 0.2 mg/kg/dose (Maximum 10 mg) po q4h prn

- Morphine should be titrated to effect usually in the dose range of 0.1-0.5 mg/kg/dose po q4h prn for infants greater than 6 months of age, children and adolescents.[3]
- Consult a pediatric dose reference for the following information if applicable:
    - The recommended dose for infants less than 6 months of age (risk of respiratory depression may be higher in this group and lower doses are required)
    - The dose recommended in renal impairment
    - The recommended intravenous dose (intravenous doses of morphine are different than oral doses)
- Oral morphine syrup is preferred for ease of administration in those patients unable to swallow immediate release tablets.
- An outpatient prescription of morphine requires a triplicate prescription in Alberta.
- In an unusual circumstance when an alternative to morphine may be required, consider hydromorphone oral solution or tablets. Consult an appropriate pediatric reference for information pertaining to dose and administration. An outpatient prescription of hydromorphone requires a triplicate prescription.
- The metabolism of oxycodone is highly variable because of genetic polymorphisms and drug-drug interactions.[4] Because of this, and the lack of a liquid dosage form for small children, oxycodone is not a first-line opioid alternative. An outpatient prescription of oxycodone requires a triplicate prescription.
- Tramadol (Tramacet®) is metabolized in a similar manner as codeine, which is also impacted by genetic polymorphism. Therefore, tramadol (or Tramacet®) is not an appropriate alternative to codeine.

Selected References:
1. MacDonald N and SM MacLeod. Has the time come to phase out codeine? [editorial]. CMAJ 2010. 182(17): 1825.
2. Kelly LE, Rieder M, van den Anker J, Malkin B, Ross C et al. More codeine fatalities after tonsillectomy in North American children. Pediatrics 2012. 129: e1343-1347.
3. Lexi-Comp Online, Pediatric Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2013; March 19, 2013.
4. Samer CF, Daali V, Wagner M, and Hopfgartner G et al. Genetic polymorphisms and drug interactions modulating CYP2D6 and CYP3A activities have a major effect on oxycodone analgesic efficacy and safety. Br J Pharm 2010. 160(4): 919-930