

# Use of Codeine in Children

Codeine is a weak opioid analgesic used in the treatment of moderate pain. Codeine is one of a number of oral opioids on the Hospital for Sick Children Formulary including morphine, hydromorphone and oxycodone.

In September 2009, the Drugs and Therapeutics committee recommended to remove codeine and all codeine-containing products from the hospital formulary due to efficacy and safety concerns.

## Codeine and genetic polymorphism:

### Key messages

- Codeine must be metabolized to its active metabolite, morphine, for its therapeutic effect. A significant proportion of the population are poor or rapid metabolizers of codeine due to genetic differences in metabolism. As a result, they experience unpredictable opioid analgesic effects or adverse effects.
- Codeine has a minor effect on its own and depends on conversion to morphine by CYP2D6 enzymes in the liver for most of its analgesic effect. As such, giving codeine is an unreliable means of giving a low dose of morphine.<sup>1,2</sup>
- Codeine has variable efficacy due to a high degree of CYP2D6 genetic polymorphism and is ineffective in up to 10% of the population who are poor metabolizers
  - 6-10% of Caucasians, 0.5 to 1% of Asians and Hispanics, 1% of Arabs, and 3% of African Americans are poor metabolizers<sup>1</sup>

## Safety concerns with codeine

- There have been growing safety concerns of codeine toxicity in ultra-rapid metabolizers
  - Ultra-rapid metabolizers convert codeine to morphine more rapidly and completely than the general population. They have plasma levels of morphine 50% higher than normal, leading to dose-related opioid adverse effects<sup>1</sup>
  - It is difficult to predict who is an ultra-rapid codeine metabolizer. Genetic tests are available on the market but are not widely accessible outside of the research setting.
  - Individuals carrying the ultra-rapid metabolizer genotype are found in about 3% of the northern European white population, between 5 and 10% in southern European populations and between 10 and 30% in Arabian and northeast African countries<sup>1</sup>
  - Toxicity is related to both dose and duration of codeine use (even low doses of codeine can accumulate after prolonged use)
- Codeine may interact with drugs that affect the CYP2D6 system
  - 2D6 inhibitors (antiarrhythmics, antidepressants, neuroleptics) may reduce codeine effectiveness while 2D6 inducers (some anticonvulsants) may increase codeine toxicity

## Reports of codeine toxicity in ultra-rapid metabolizers...

### *Apnea in post-tonsillectomy patients*

- A recently published case report documented the death of a previously healthy 2 year old boy after elective tonsillectomy for obstructive sleep apnea.<sup>3</sup>
- Although the post-op codeine dose was within normal range (1-3 mg/kg/day), increased conversion of codeine to morphine due to ultrarapid metabolism resulted in a toxic accumulation of morphine, leading to respiratory depression and death. There have been other similar reported deaths.

### *Breast-feeding mothers*

- Codeine products are commonly used to manage post-partum pain
- In October 2008, Health Canada issued a safety alert that nursing mothers who are rapid-metabolizers may have higher morphine levels in their breast milk when taking codeine. These higher than expected levels of morphine in breast milk may lead to life-threatening or fatal side effects in nursing their nursing infants.<sup>4</sup>
- Recent research from Motherisk suggests that codeine may not be safe for all mothers of nursing infants, as in a minority of cases it may cause CNS depression and apnea and death.<sup>5,6</sup>

### *Other patients*

- In adults who are ultra-rapid metabolizers, even small doses of codeine have lead to loss of consciousness and respiratory failure requiring naloxone infusion. Blood levels of morphine were 20 to 80 times as high as the blood level that would have been expected on the basis of measurements in healthy persons with extensive CYP2D6 metabolism.<sup>7</sup>

## What can be used instead of codeine?

There are several other oral opioids that can be used instead of codeine in children. The efficacy and safety are the same as codeine as long as an equipotent dose is used.

### Opioid Equianalgesic Conversion Chart

Drug	Equipotent PO dose <sup>8</sup>	Dosing <sup>8</sup>
Codeine	200mg	0.5-1mg/kg/dose po q4-6h, max 30-60mg/dose
Morphine	Acute: 60mg Chronic: 30mg	0.2-0.5mg/kg/dose po q4-6h, max 15mg/dose
Hydromorphone	Acute: 6-7.5mg Chronic: 4-6mg	0.04-0.08mg/kg/dose po q3-4h, max 2-4mg/dose
Oxycodone	20-30mg	0.05-0.15mg/kg/dose po q4-6h, max 5-10mg/dose

- Low-dose morphine can be used instead of codeine. Morphine is available as an oral liquid, short-acting and long-acting capsules and tablets in multiple strengths to allow for flexible dosing options
- Oxycodone is another option for children who require a weak opioid who are old enough to take tablets. Oxycodone combination products (e.g. Oxycocet<sup>®</sup>) can be used as alternatives to codeine combination products (e.g. Tylenol #3<sup>®</sup>).

**Key point:** Codeine is less potent than morphine with only 10% of codeine converted to morphine. The conversion ratio of PO codeine to PO morphine with chronic dosing is roughly 10:1

## Common Misconceptions About Codeine

### **Codeine has a lower incidence of opioid-related side effects compared to stronger opioids**

- **False** – there is little evidence to confirm that the side effects of codeine are significantly fewer or less severe than other opioids when used at equipotent doses. Purported benefits of lower incidence of CNS and respiratory depression have been noted after single doses of codeine although they may not exist after repeated dosing.

### **Codeine is an effective analgesic for acute, post-operative pain**

- **Not necessarily.** Single-dose studies in adults have shown no difference between codeine and placebo.
- In randomised, double-blind, single-dose studies in patients with moderate to severe pain, a 60 mg oral dose of codeine had an number needed to treat (NNT) of 16.7 for at least 50% pain relief over 4 to 6 hours compared with placebo. This means that for every 17 patients who receive codeine, one patient will get at least 50% relief (the other patients may or may not obtain relief but it does not reach the 50% level).<sup>9,10</sup>
- In a systematic review of randomized controlled trials comparing a combination of acetaminophen and codeine with acetaminophen alone in postoperative pain, the additional analgesic effect of 60 mg of codeine added to acetaminophen was 12 extra patients in every 100 achieving at least 50% pain relief. This was an NNT for adding codeine 60 mg of 9.1 (5.8–24).<sup>11</sup>

For more information, please contact the SickKids Drug Information Service at 416-813-6703.

## References:

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- <sup>9</sup> Moore RA, McQuay HJ. Single-patient data meta-analysis of 3453 postoperative patients: Oral tramadol versus placebo, codeine and combination analgesics. *Pain* 1997; 69:287-294.
- <sup>10</sup> Oxford League Table of Analgesic Efficacy in Acute Pain  
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