Proposal for deletion

**Codeine phosphate tablets for pain in children**

**Introduction**

Codeine is a phenanthrene opioid derivative. It is listed in the 2010 WHO Model List of Essential Medicines for Children and in the 2010 WHO Model Formulary for Children to be used as analgesic for pain relief. Codeine phosphate has been recommended and widely used for the relief of moderate pain in children. WHO has undertaken the update of the 1998 *WHO Guidelines on Cancer Pain Relief and Palliative Care in Children* and extended the scope to other medical diseases and conditions. The request for deletion of codeine arises from the recommendations issued in the *WHO Guidelines on Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses* (currently under review by the WHO Guidelines Review Committee).

**Product and Dosage**

Codeine phosphate is listed as a 15 mg tablet. The dosage for pain relief in neonate, infants and children reported in the WHO Model Formulary for Children is "0.5–1 mg/kg every 4–6 hours when needed; maximum 240 mg daily".

**Evidence of value**

The Guidelines Development Group of the *WHO Guidelines on Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses*, after review of available evidence and considerations on well-known genetic variability in biotransformation (CYP2D6) has excluded codeine from the pain treatment algorithm.

Codeine is a pro-drug that is converted into its active metabolite morphine by the enzyme CYP2D6. In the foetus, the CYP2D6 activity is absent or less than 1% of adult values. It increases after birth, but it is estimated to be no higher than 25% of the adult values in children below 5 years. As a consequence, the analgesic effect of codeine is (very) low or absent in neonates and young children. Furthermore, there is considerable pharmacogenetics variability among populations. The percentage of poor metabolizers can vary in ethnic groups from 1% to 30%, resulting in ineffectiveness in large numbers of patients, both adults and children.\(^1,2\) There are also individuals who are ultra fast and extensive metabolizers of codeine and are at risk of severe opioid toxicity, given the high and uncontrolled conversion of codeine into morphine.\(^3\)

The efficacy or safety problems of codeine in an unpredictable proportion of the paediatric population does not make it a recommended medicine for pain relief. There is indeed a considerable risk that, if administered, it won’t be effective and will leave a child in unnecessary pain when other effective and non costly medicines exist (morphine). Furthermore, its efficacy does not appear to be superior to ibuprofen as reported in the few studies conducted in acute pain setting.\(^4,5\)

The Guidelines Development Group recommended a two step approach as an effective strategy for the pharmacological management of persisting pain in children with medical illness, based on the consideration that it presents higher degrees of certainty of effectiveness in children than the analgesic ladder in three steps introduced by WHO in
1986. The three-step analgesic ladder recommended the use of codeine as a weak opioid for the treatment of moderate pain, while the two-step approach considered the use of low doses of morphine for the treatment of moderate pain. Annex 1 documents the rationale (including review of evidence) for the recommendation of a two-step approach and the exclusion of codeine from the pain treatment algorithm for children. Annex 2 reports a GRADE table on a Randomized Control Trial in acute pain comparing efficacy of codeine, paracetamol and ibuprofen. 

Recommendations

Codeine phosphate should be deleted from the WHO Model List of Essential Medicines for Children for its use as an analgesic. The rationale for the recommendation not to use codeine for relief of persisting pain in children is applicable and valid for acute and procedural pain. Furthermore, the WHO Model List already includes morphine which is now recommended by WHO for relief of moderate to severe persisting pain in children.

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Secretariat for the development of the WHO Guidelines for Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses

References

4 Clark E, et al. A randomised controlled trial of acetaminophen, ibuprofen and codeine for acute pain relief in children with musculoskeletal trauma. Paediatrics 2007; 119; 460-7
ANNEX 1. CLINICAL RECOMMENDATIONS

ANALGESIC LADDER: TWO-STEP APPROACH VERSUS THREE-STEP APPROACH

Recommendations

- The panel recommends the use of treatment in two steps rather than treatment in three steps for the management of persisting pain in children with medical illnesses.  
  *Strong recommendation, very low quality of evidence.*

Domains and considerations

**Quality of evidence**
There are no formal comparisons between the two-step and three-step treatment approaches in children. The two potential medicines that might appear in the second step, each present challenges in children.  
Tramadol is generally not registered for use in children below 12 years, as evidence of efficacy and safety is not available and has not been submitted for evaluation by medicines regulatory agencies.  
Codeine presents with well-known safety and efficacy difficulties related to genetic variability in biotransformation (CYP2D6), although it is registered for use and has been widely used in children.  
Uncertainty: Yes, for the three-step pharmacological pain treatment approach.

**Risks/Benefits**

**Benefits**
The potential benefit of access to effective opioid analgesics outweigh the benefits of codeine in this age group.

**Risks**
The risks associated with strong opioids are recognized, but are acceptable in comparison to the uncertainty associated with codeine and tramadol.  
Uncertainty: If there is new evidence for tramadol or an alternative (intermediate potency opioid), then this benefit risk assessment can be reconsidered.

**Values and acceptability**

**In favour**
The panel placed high value on effective treatment of pain.

**Against**
The panel acknowledged continuing barriers to access to strong opioids in many settings, but a strong recommendation in this regard could overcome this negative sentiment and promote wider access to opioids for pain relief.  
Uncertainty: None.
Cost
Although tramadol is now off patent in many markets and generics have been launched, the problem of market authorization for children remains in several countries. Codeine is widely available and inexpensive, but presents with potential lack of efficacy and/or safety problems in an unpredictable proportion of patients. Although access to strong opioids is variable, price is not generally a significant barrier. Uncertainty: None.

Feasibility
Child appropriate dosage forms for opioids are available with the exception of very young infants. Liquid preparations allow for easier dose titration, but concern about cost, stability, portability and storage remain.
The dosage forms reported on the 2010 EMLc are the following:
Granules: modified release (to mix with water), 20 mg, 30 mg, 60 mg, 100 mg, 200 mg
Injection: 10 mg (morphine hydrochloride or morphine sulfate) in 1-ml ampoule.
Oral liquid: 10 mg (morphine hydrochloride or morphine sulfate)/5 ml.
Tablet: 10 mg (morphine sulfate).
Tablet (prolonged release): 10 mg; 30 mg; 60 mg (morphine sulfate).
Strong opioids are not available in all countries. Uncertainty: None.

Policy and research agenda
Firstly, research on potential alternative to codeine as a second step in a three-step approach is needed.
Second, a reconsideration of the inclusion of codeine in the EMLc shall be encouraged.
Thirdly, long-term safety data of NSAIDs and paracetamol is needed.
Annex 2. GRADE Tables

GRADE Table 1A

**Author(s):** Wiffen PJ  
**Date:** 2009-04-16  
**Question:** Should Paracetamol vs. Ibuprofen be used in Children with musculoskeletal trauma (acute pain). Mean age: approximately 12 years  
**Settings:** Emergency department. Ottawa Canada  
**Bibliography:** Clark E, Plint A et al. A randomised controlled trial of acetaminophen, ibuprofen and codeine for acute pain relief in children with musculoskeletal trauma. Paediatrics 2007; 119; 460-7

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**Pain relief measured as reduction in VAS at 60 mins (follow-up 120 minutes; measured with: VAS Pain; range of scores: 0–100; Better indicated by lower values)**

**Minor adverse events (such as nausea, sleepiness, constipation)**

| 1 | randomized trial | no serious limitations | no serious inconsistency | serious² | no serious imprecision | Gastrointestinal bleeding is not reported | 8/104 Paracetamol 11/101 Ibuprofen | LOW |

¹ Study in acute pain setting. Doses: paracetamol 15mg/kg (max 650mg), ibuprofen 10mg/kg (max 600mg). Data extracted as reported.  
² Acute pain study. No significant difference between groups for adverse effects  
**ITT:** intention to treat
**GRADE Table 1B**

**Author(s):** Wiffen PJ  
**Date:** 2009-04-16  
**Question:** Should Ibuprofen vs. Codeine be used in Children with musculoskeletal trauma (acute pain). Mean age: approximately 12 years  
**Settings:** Emergency department. Ottawa Canada  
**Bibliography:** Clark E, Plint A et al A randomised controlled trial of acetaminophen, ibuprofen and codeine for acute pain relief in children with musculoskeletal trauma. Paediatrics 2007; 119; 460-7

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Pain relief measured as reduction in VAS at 60 mins (follow-up 120 minutes; measured with: VAS Pain; range of scores: 0--100; Better indicated by lower values)

| 1 | randomized trial | no serious limitations | no serious inconsistency | serious¹ | no serious imprecision | None | Paracetamol 112(ITT) | Codeine 112(ITT) | - | Paracetamol mean 12 lower (16 to 8 lower) Codeine 11 lower (16 to 5 lower) | LOW |

Minor adverse events (such as nausea, sleepiness, constipation)

| 1 | randomized trial | no serious limitations | no serious inconsistency | serious² | no serious imprecision | The variability in biotransformation of codeine not considered | 8/104 Paracetamol 8/104 Codeine | LOW |

¹ Study in acute pain setting. Doses: paracetamol 15mg/kg (max 650mg), codeine 1mg/kg (max 60mg).  
Data extracted as reported.  
² Acute pain study. No significant difference between groups for adverse effects  
ITT: intention to treat