Reducing codeine use in paediatric pain management

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Background

- Codeine metabolised to morphine by CYP2D6

- Toxicity due mainly to opioid effects
  - respiratory depression
  - circulatory depression, respiratory arrest, shock, and cardiac arrest

- Genetic polymorphism

- Pharmacokinetic & pharmacodynamic studies in children are lacking

- Global movement to restrict codeine use since 2006
International Timeline

- **2007**
  - UK safety warning

- **2009**

- **2012**
  - Aug '12: FDA safety warning
  - May '12: Pediatrics, Ciskowski et. al, publish codeine death in 2 yr old

- **2013**
  - Feb '13: FDA Boxed Warning + Contraindication
  - Oct '14: RCH (Melbourne) move to reduce codeine use in children
  - July '13: UK release restrictions
  - Oct '14: TGA release
  - Oct '15: TGA release

- **2014**
  - '13 NPS Safety warning

- **2016**
  - Feb '16: PMH restricts codeine

- **2006**
  - Neonatal death
    - Breastfeeding mother was an ultra rapid metaboliser

- **2009**
  - NEJM: Ciskowski et. al, publish codeine death in 2 yr old

- **2007**
  - Codeine deaths

- **2013**
  - EMA PRAC restrict codeine

- **2015**
  - PMH discuss codeine
Codeine in practice

• Studies
  • comparable efficacy of codeine with other active treatments
  • musculoskeletal NSAIDs equal or better efficacy compared to codeine/paracetamol

• Enzymatic metabolism fully matured by age 12
• CYP2D6 genotyping prior to analgesic therapy ideal
  • Impractical in clinical practice
  • 1 functional allele - extensive metaboliser
  • Duplication or multi-duplications of CYP2D6 gene - ultra-rapid metaboliser

• Response to codeine not directly correlated with phenotype
• Close monitoring for signs of opioid toxicity critical
Case 1

- 4-year-old boy, native American
- 27.6 kg
- Tonsillectomy + adenoidectomy
- Hx obstructive sleep apnoea & recurrent tonsillitis
- Uneventful overnight stay
- Discharged with codeine 8 mg per dose, up to 5 doses a day prn

Prescribed/administered dose appropriate.

“His ultrarapid metaboliser CYP2D6 status resulted in an increased morphine leading to respiratory arrest.

Postmortem analysis revealed the cause of death to be bilateral acute bronchopneumonia as a consequence of codeine and morphine toxicity after adenotonsillectomy.”

Respiratory depression has been shown in young children with serum morphine concentrations exceeding 20ng/mL.
Case 2

- 3-year-old girl (14.4 kg) of Middle Eastern descent
- Tonsillectomy for obstructive sleep apnoea
- In hospital 2x 15 mg doses of codeine syrup
- Discharged with paracetamol 150mg/codeine 15 mg every 4 to 6 hours prn
- >6 hours after 4th codeine dose found unresponsive with a fever of 100°F (37.8°C)

**Recommendation**

Prescribed/administered dose appropriate.

‘Her genotype was determined to be an extensive metaboliser of CYP2D6. In this case, her morphine levels suggested ultra-rapid metabolism, which was not consistent with her genotype.

Extensive metaboliser genotype often overlaps with the ultrarapid metaboliser phenotype.’
Case 3

- 5-year-old boy (29 kg)
- bilateral myringotomy tube insertion, tonsillectomy & adenoidectomy for recurrent tonsillitis & snoring
- Post-op prescribed paracetamol & 12mg codeine every 4 hours
- Found without vital signs by his mother 24 hours after surgery

- Postmortem
  - codeine concentration 79 ng/mL
  - morphine concentration was 30 ng/mL

The codeine levels are consistent with prescription of 0.41 mg/kg every 4 hours as needed i.e. within the recommended dosing range.

‘It is highly likely that the child was a CYP2D6 ultra-rapid metaboliser given his exceedingly high morphine concentration relative to codeine.’
1969 to May 2012
13 paediatric cases associated with codeine toxicity
  • 10 deaths
  • 3 overdoses
  • 21 months to 9 years of age
  • tonsillectomy & adenoidectomy 8 cases
  • respiratory tract infection 3 cases
  • children appeared to receive appropriate doses of codeine

CYP2D6 metaboliser status mentioned in 7 cases described in the literature
  • 3 children ultra-rapid metabolisers
  • 3 extensive metabolisers
  • 1 likely ultra-rapid metaboliser
European Medication Authority Investigation

Paediatric Literature
• 5 cases toxicity in post-tonsillectomy for obstructive sleep apnoea
• 1 case non-fatal case reported in 1997

Pharmacovigilance
10 fatal cases attributed to codeine for analgesia in children
• 1 accidental overdose
• 2 to 17 years of age
• Toxic morphine levels were reported in 4 cases
• 2 cases children dosage in range
• Genotype/phenotype was not available
TGA

Pharmacovigilance

• 14 cases respiratory depression post-codeine (all ages)
• 5/14 fatal
• No fatalities in children <18 years
• 1 non-fatal respiratory depression in 16 yr old after taking codeine
Australian recommendations

Do not use codeine to treat pain in children aged under 18 after tonsillectomy and/or adenoidectomy. Consider alternative analgesics.

Only use codeine to treat moderate pain of short duration in children over 12 years and only if it cannot be relieved by other analgesics such as paracetamol or ibuprofen.

Do not use codeine in adults or children known to be ultra rapid metabolisers of codeine.

If codeine is prescribed, use the lowest dose for the shortest time possible. Avoid round the clock dosing.

If codeine is prescribed, advise parents or carers to monitor for signs of morphine toxicity (such as unusual sleepiness, confusion, small pupils, nausea or vomiting, constipation, lack of appetite or difficult or noisy breathing) and seek immediate medical attention if these occur.

Report adverse events to the TGA.
Role of codeine at PMH

paracetamol
NSAIDs

tramadol 1-2 mg/kg

codeine 0.5-1mg/kg or

morphine
or
oxycodone
0.05-0.1mg/kg

0.05-0.1mg/kg

0.5-1mg/kg or
CAHS Recommendations

Only children for whom the benefits outweigh risks receive codeine for moderate to severe pain.

Codeine for treatment of acute moderate to severe pain in children above 12 years of age, where simple analgesics are ineffective.

Codeine contraindicated in children <18 years who undergo tonsillectomy and/or adenoidectomy with a history of obstructive sleep apnoea.

Prescriptions of codeine to include dosing interval & the duration of use.
Change management

• Patient groups affected
  – ED discharge (previously Painstop Day-time®)
  – Post-op T&A
  – Chronic pain management (minimal use)

• No ideal alternatives
  – Access: OTC vs prescription, PBS volume for short duration Tx
  – Potency: tier 2 analgesia
  – Formulation: tramadol, morphine vs oxycodone in diversion
  – Oxycodone: off-label, limited post-marketing toxicity data

• Community interest in PMH decision
• Logistics of schedule 8 pre-packs
Practice changes

• Cautious advice to community enquiries

• Risk reduction measures
  • Post-T&A
    • promoted equitable analgesia from NSAIDs
    • oxycodone
      • limited volume dispensed on d/c
      • Anaesthetists to prescribe
      • 1st dose + 1 hour obs prior D/c

• ED to supply oxycodone on d/c at 0.05mg/kg initially
  • small volume pre-packs in after-hours
  • patient information leaflets prepared
  • education to ED doctors

• Reduce imprested codeine products
Thank-you to PMH APS, Clinical Pharmacy, MSRG and DTC.

References
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