



Codeine and Paracetamol in Paediatric use, an Update

5th October 2013

This guidance should be read in parallel to the detailed guidelines on pain management in children (APA guidelines) 2nd edition. This can be found In Pediatric Anesthesia Good Practice in Postoperative and Procedural Pain Management 2nd Edition 2012 Volume 2 Supplement 1 pages 1-79.

Codeine has been used widely for many years both within and without hospital and as a treatment for breakthrough pain when paracetamol and an NSAID are not sufficient. As a result of recent evaluations of its benefit/safety profile following several documented deaths in children, the advice on the use of the drug in both the USA and Europe has changed. Prior to the announcement by the MHRA on 28th June 2013, the entry on codeine in the BNFC stated that it could be used for mild to moderate pain, that tablets were unlicensed for children under 12 and that injections were unlicensed for children under 1 year. Indications and dosages for neonates, infants and children were provided. In the UK codeine has been a popular drug for second line analgesia particularly after tonsillectomy. Now following the FDA and EMA inquiries, the MHRA have issued a press release on the use of codeine in children:

<http://www.mhra.gov.uk/home/groups/comms-po/documents/news/con287049.pdf>).

The key points from this press release, is advice that:

1. Codeine should not be used in any children (under 18 years of age) who undergo removal of tonsils or adenoids due to sleep apnoea
2. Codeine should only be used in children over 12 years of age

Given the widespread use of this drug in paediatrics and postoperative analgesia particularly after day stay surgery, this has caused considerable concern. The current advice falls short of contraindicating the use of codeine in all children but has left the clinicians with a dilemma to either continue to use the drug with increased caution in the knowledge of the

MHRA communication or to change practice to one of a number of alternatives such as oral morphine, tramadol, oxycodone or dihydrocodeine.

To date, individual paediatric teams have carried out a risk assessment (formally or informally) and on that basis have either continued cautiously with codeine or explored the alternative drugs and how to use them effectively and safely. The decisions have been based largely on personal and institutional experience of different drugs, the ability to provide formulations of the alternatives, and the local Trust attitudes to the MHRA communication. There are many paediatric drugs which are used “off licence” and there are some drugs that are used with caution by clinicians despite contraindication by the MHRA. However the phrase “should only be used in children over 12 years of age” implies that it should not be used in children under 12 years of age. This has increased concern in those still intending to use codeine.

At present there is no consensus or quality data on how best to provide safe and effective postoperative analgesia at home when paracetamol and NSAID’s are insufficient. Furthermore while codeine is contraindicated in all children after tonsillectomy/adenotonsillectomy in those suffering from sleep apnoea, it is unclear if other opioids provide any greater margin of safety in this context. Nevertheless, children who have tonsillectomy, adenotonsillectomy, orchidopexy and other procedures on a day stay basis commonly experience pain after discharge that is not effectively managed with the simpler analgesics.

In addition, recent considerations by the College of Emergency Medicine have led to the paradox that postoperative paracetamol dosing can breach the threshold for therapeutic overdose and consideration for treatment with N-acetyl cysteine. Below is a summary of the current issues with these two drugs. This is followed by practice points and recommendations to help guide individual paediatric practice. The aim is that this brief document adds some background, clarity and advice that can be used in addition to the APA pain guidelines and the specific information in the BNFc. As described above, different specialist paediatric hospitals have approached the problem according to their skills and knowledge in collaborations with their pharmacists. We would recommend that anaesthetists who are practicing outside of a specialist unit may find discussion with the local regional centre beneficial and supportive. The expertise may be useful in implementing a regional networked approach to maintain a good benefit safety profile while new evidence based guidance is obtained.

Codeine

- Codeine remains in the APA pain guidelines as a weak opioid for treatment of moderate pain. It is described for use on its own and in combination with other agents such as paracetamol or NSAID's.
- The FDA in the US is warning against the use of Codeine for children and adolescents having adenoidectomy or tonsillectomy surgery that suffer from obstructive sleep apnoea. In the 4 cases reported (3 deaths and one life threatening event). The doses taken were within prescribed limits and occurred after more than 1 day. The European Medicines Agency (EMA) and MHRA have also considered the evidence and have issued guidance on the use of codeine. In their Press release of 28th June 2013 it states that codeine should not be used in any children who undergo removal of tonsils or adenoids due to sleep apnoea. It also recommends that codeine should not be used in children under 12 years of age.
- At the heart of the problem are the issues of alteration in respiratory drive associated with obstructive sleep apnoea and variation in metabolism of codeine in different genetic groups. Of particular concern is the significance of fast metabolisers who represent up to 0.7% of the general population but up to 30% of children Middle Eastern and African/Ethiopian descent:
(Tremlett M. Editorial: *Whither Codeine?* in *Paediatric Anaesthesia* 2013 <http://onlinelibrary.wiley.com/doi/10.1111/pan.12190/pdf>). The metabolism to morphine can be accelerated in these individuals leading to accumulation. However the role of the parent drug and other metabolites remains unclear.
- Clearly children who have had tonsillectomy need analgesia for moderate and sometimes severe pain at home after surgery. Paracetamol and ibuprofen will not always provide enough efficacy and choices are limited. Commonly used protocols for management of tonsillectomy after surgery have codeine as one of the co-analgesic drugs both within the hospital and after discharge from hospital as rescue treatment for breakthrough pain when paracetamol and NSAID's are not sufficient.
- Oral morphine, tramadol and oxycodone are alternatives to codeine. Tramadol is unlicensed for children under 12 years of age in the UK. Oxycodone is unlicensed in all children although doses are described for pain in palliative care. Low strength oral morphine (10mg/5ml) and tramadol are prescription only medications rather than over the counter and therefore would need to be either given to patients in packs or via a prescription. Additionally tramadol is likely to become a controlled drug in the near future making prescription for home use more complex. The higher concentration of morphine (100mg/5ml) is a controlled drug, which presents further problems and is not appropriate for weight based dosing in children.

- There is little guarantee or evidence base that these alternative opioids are safer than codeine: indeed morphine is a high efficacy drug and if given to parents without careful supervision/instruction the potential for overdose may be significant. Current dosing guidelines for oral morphine in 2-12 years old is 100 -200micrograms/kg every 4 hours according to response (see BNFC). Most practitioners are restricting the higher dose (200microgrames/kg) to in-hospital care only.
- A distinction needs to be made between analgesia used within the hospital and prescribed drugs for parents to administer after discharge. In the hospital setting with greater control and monitoring it is usually possible to safely use higher doses.
- Some Trusts are moving to take home drugs that are not relabelled with specific physician based prescriptions. The packaging will then simply have the standard dosing information. These dosing instructions are conservative and may result in suboptimal analgesia even when taken as directed.
- There is limited information on the use of dyhydrocodeine

Additional Practice Points for Codeine

The current recommendations within the APA guidelines on the use of codeine in paediatric practice are:

Codeine

Codeine is much less efficacious than morphine and is used for the relief of mild to moderate pain. It is often given in combination with NSAIDs or paracetamol. Codeine can also given by intramuscular injection, in doses similar to those by mouth, the intravenous route should not be used as severe hypotension may occur.

The analgesic effect of codeine is unpredictable. Its effects may be wholly or mainly due to metabolism to morphine. The enzyme responsible for this conversion, CYP2D6, shows significant genetic variation and across populations the amount of codeine converted to morphine is very variable (Williams et al. 2002). Development may also affect CYP2D6 activity with lower levels of activity found in neonates and infants.

Codeine dosing schedules:

Oral, intramuscular or rectal:

Neonate or Child: 0.5-1 mg/kg 4-6 hourly (care with repeated doses in neonates)

1. Opioids may be required for second line analgesia in cases where the combination of paracetamol and a NSAID are inadequate. This can represent a problem in that dosing after discharge may not be followed by parents or carers. Inadequate dosing may result in avoidable pain while excess dosing risks adverse events that include respiratory depression or even respiratory arrest. All currently used opioids including codeine can be associated with this complication and all opioids can be highly variable in their clinical effects due to individual pharmacokinetic and

pharmacodynamic factors. Children with proven obstructive sleep apnoea are a particularly vulnerable group in that they may have disturbed ventilatory function, which can be exacerbated by opioids. Currently available opioids include codeine, oral preparations of morphine, oxycodone, dihydrocodeine and tramadol. The Paediatric Pain Travelling Club has indicated that at present codeine represents a drug that remains in common usage for pain at home in the UK. This view is supported by the recently completed pain at home prospective audit, which was completed prior to the EMA and MHRA statements.

2. A history of prior experience with codeine should be sought, including: efficacy, side effects and family history of adverse events. If opioids have been used within the hospital setting before discharge from hospital, consideration should be given to their response to the drug.
3. Recent fatalities following adenotonsillectomy for OSA have been reported in children who are ultra-rapid metabolisers of codeine. Problems can arise even after uneventful overnight stays on reduced dose liquid codeine: adverse events and fatalities have been reported after further dosing at home in children with an ultra-rapid metabolizer genotype (*Kelly LE, Rieder M, Van den Anker J et al. More codeine fatalities in North American Children. Pediatrics 2012 129(5): 1343-7*). As a result of the published data and the press release from the MHRA it is advised that codeine should not be administered outside the hospital in children with proven sleep apnoea from sleep studies or a strong history of respiratory symptoms during sleep (observed airway obstruction and or respiratory pause). In any event, the dose of any opioid should be adjusted in children with OSA and the response monitored in hospital prior to discharge (*Khetani JD, Madadi P, Sommer DD et al. Apnoea and oxygen desaturation in children treated with opioids after adenotonsillectomy for obstructive apnoea syndrome: a pilot study. Paediatric Drugs 2012. 14(6); 411-5*).
4. Codeine should be administered with extreme caution outside the hospital in infants. Neonates and young infants may have immature pharmacokinetic and pharmacodynamic profiles that influence both dose-dependent efficacy and side effects.
5. Codeine may be considered as a second line analgesic drug for use outside hospital when paracetamol and an additional NSAID are likely to provide inadequate analgesia.
6. Alternate drugs such as oral morphine, tramadol and oxycodone are likely to replace the use of codeine with time as experience with these grows and more appropriate formulations become available.

7. Prescriptions of codeine may be outside the recommendations of the regulatory authorities (MHRA). Drugs use may be “not recommended” or “contraindicated”. It is therefore important to consider local and individual responses and policies to the regulatory issues.
8. Parent education on the correct use of opioids should be provided before the child is discharged from hospital, including written instructions regarding formulation, dose and frequency of administration.

Paracetamol

- Dosing recommendations for paracetamol have recently come under scrutiny. On the 3rd September 2012, The Medicines & Healthcare Products Regulatory Agency (MHRA) in collaboration with the College of Emergency Medicine published new guidance on paracetamol dosage following a review by the Commission on Human Medicines of the treatment of paracetamol poisoning. Professor Simon Thomas chaired the implementation group, with input from the National Poisons Information Service (NPIS). Details can be found on:
<http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON185624>
Their recommendation was that doses greater than 75mg/kg/day should be considered as a “staggered overdose”. The management of this “overdose” included consideration of treatment with N-Acetylcysteine. This has necessitated reconsideration of current guidelines within the APA pain guidelines and also the BNFC, which states that the higher doses quoted for severe symptoms are unlicensed but provides dose information for physicians. This quotes oral doses of up to 90mg/kg/day in children 1month to 12 years of age.
- We have consulted Brian Anderson in New Zealand who has run a series of simulations with 75 and 90mg/kg/day. This would suggest that the benefit of 90mg/kg/day over 75mg/kg/day is minimal. However, administration of 15mg/kg/dose on a 4 -6 hourly basis to achieve 75mg/kg/day could be impractical for a child who may be sleeping.
- A distinction needs to be made between analgesia used within the hospital and prescribed drugs for parents to administer after discharge. In the hospital setting with greater control and monitoring it is usually possible to safely use higher doses for a restricted time period.
- Some Trusts are moving to take home drugs that are not re-labelled with specific physician based prescriptions. The packaging will then simply have the standard dosing information. These dosing instructions are conservative and may result in suboptimal analgesia even when taken as directed.
- An additional and separate consideration with paracetamol has been the upper recommended limits of intravenous paracetamol following a number of adverse events from paracetamol administration. These are predominantly related to errors of prescribing (e.g. use ml/kg instead of mg/kg).

Additional Practice Points for Paracetamol

The current entry in the APA guidelines for oral and rectal paracetamol as found in the APA guidelines 2nd Edition published in Pediatric Anesthesia July 2012 Volume 22 supplement 1: 1-79

Age	Route	Loading dose (mg·kg ⁻¹)	Maintenance dose (mg·kg ⁻¹)	Interval (h)	Maximum daily dose (mg·kg ⁻¹)	Duration at maximum dose (h)
28-32 weeks	Oral	20	10-15	8-12	30	48
	Rectal	20	15	12		
PCA	Oral	20	10-15	6-8	60	48
	Rectal	30	20	8		
>3 months	Oral	20	15	4	90	48
	Rectal	40	20	6		

PCA, postconceptual age.

Current BNFC Recommendations for severe pain are:

By mouth

Child 1 month–6 years 20–30 mg/kg as a single dose then 15–20 mg/kg every 4–6 hours; max. 90 mg/kg daily in divided doses

Child 6–12 years 20–30 mg/kg (max. 1 g) as a single dose then 15–20 mg/kg every 4–6 hours; max. 90 mg/kg (max. 4 g) daily in divided doses

Child 12–18 years 1 g every 4–6 hours (max. 4 doses in 24 hours)

By rectum

Child 1–3 months 30 mg/kg as a single dose then 15–20 mg/kg every 4–6 hours; max. 90 mg/kg daily in divided doses

Child 3 months–6 years 30–40 mg/kg as a single dose then 15–20 mg/kg every 4–6 hours; max. 90 mg/kg daily in divided doses

Child 6–12 years 30–40 mg/kg (max. 1 g) as a single dose then 15–20 mg/kg every 4–6 hours; max. 90 mg/kg (max. 4 g) daily in divided doses

Child 12–18 years 1 g every 4–6 hours (max. 4 doses in 24 hours)

It is likely that the recommendations in the BNFC for severe pain will remain the same.

1. The use of oral/rectal paracetamol within a hospital setting should continue as before using the APA guidelines and the BNFC recommendations.
2. It is emphasised that drug requirements and dosing schedule need to be reviewed regularly when the drug is used for greater than 48 hours.
3. Less control is available to monitor and deliver paracetamol outside the hospital setting. Consideration may be needed to reduce dosing outside the hospital setting to provide a maximum of 75mg/kg/day (15mg/kg 4-6 hourly with a maximum of 5 doses/day).
4. Parent education on the correct use of paracetamol should be given before the child is discharged from hospital. This includes written instructions regarding formulation, dose and frequency of administration.
5. Children need to be considered individually and dosing adjusted accordingly. This includes children who are debilitated or dehydrated. Children who are severely overweight may require a modest reduction in paracetamol doses to reflect that their lean body mass does not reflect their weight.
6. The BNFC also provides recommendations for oral paracetamol dosing by age and while these doses are usually less than that prescribed for severe pain they may be a useful additional guide.

Intravenous Paracetamol

Current entry in the APA pain guidelines 2nd edition is:

Weight (kg)	Dose	Interval (h)	Maximum daily dose
<5 (term neonate)	7.5 mg·kg ⁻¹	4-6	30 mg·kg ⁻¹
5-10	10 mg·kg ⁻¹	4-6	40 mg·kg ⁻¹
10-50	15 mg·kg ⁻¹	4-6	60 mg·kg ⁻¹
>50	1 g	4-6	4 g

Current advice published recently by the Royal College of Anaesthetists “Safe Anaesthesia Liaison Group” (SALG) is:

	Term newborn infants, infants, toddlers and children weighing <10kg*	Children weighing >10kg and <33kg	Children, adolescents, and adults weighing >33kg and <50kg	Adolescents and adults weighing >50kg
Dose of IV paracetamol (per infusion administration)	7.5mg/kg	15mg/kg	15mg/kg	1g
Maximum daily infusion dose**	30mg/kg	60mg/kg	60mg/kg	Must not exceed 4g

*The dose of IV paracetamol is controversial in neonates and infants. The BNF for Children (BNFC) suggests a dose of 7.5mg/kg every 8 hours (maximum 25mg/kg daily) in preterm neonates over 32 weeks postmenstrual age, 10mg/kg every 4-6 hours (maximum 30mg/kg daily) in neonates.⁶

These two guidance documents have very similar dosing recommendations. It is emphasised that local policy should be consistent so that a routine administration policy is provided.