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GUIDANCE FOR THE ADMINISTRATION OF CODEINE AND ALTERNATIVE OPIOID ANALGESICS IN CHILDREN ■ ■ ■

EXECUTIVE SUMMARY ■ ■ ■

- In June 2013 the advice given by the Medicines and Healthcare Products Regulatory Agency (MHRA) on the use of codeine in children changed. This response followed reports of several deaths that occurred in North America outside the hospital environment.
- The MHRA now advise that codeine should not be used in any child with a history of sleep apnoea who is undergoing tonsillectomy or adenoidectomy and that codeine should only be used in children over the age of 12 years.
- The basis of this directive is the understanding that codeine is variably metabolised to morphine and that some children (fast metabolisers) will be vulnerable to unpredictable and excessive respiratory depression particularly those who have pre-existing alteration in ventilatory drive (e.g. chronically obstructed airways from enlarged tonsils).
- Codeine has been used for many years as supplementary analgesia for children outside the hospital setting. Following the MHRA directive, hospitals and pharmacies have had to reconsider how best to find safe alternative solutions for acute pain that cannot be controlled adequately with paracetamol and non-steroidal anti-inflammatory drugs following discharge home from hospital.
- Within the UK different solutions are being employed. These include continuing to use codeine with increased caution or adopting alternative opioid medication regimens: oral morphine, dihydrocodeine, oxycodone or tramadol are potential alternatives. Guidance on the selection and use of these opioids is provided below.
- It should be emphasised that none of these alternative opioids provide the ideal solution to this difficult analgesic problem, and that for some children the length of stay in hospital may need extending to allow opioid analgesia to be provided safely.





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CHANGE IN RECOMMENDATIONS FOR THE USE OF CODEINE ■ ■ ■

Codeine has been used widely for many years inside as well as outside the hospital setting as a treatment for breakthrough pain when paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) prove insufficient or are contraindicated. As a result of recent evaluations of its benefit/safety profile following several documented deaths in children in North America, the advice on the use of the drug in both the USA and Europe has changed. Prior to the announcement by the MHRA on 28 June 2013, the entry for codeine in the children's British National Formulary (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. Historically in the UK codeine has been a popular drug for second line analgesia particularly after tonsillectomy.

Following inquiries by the American Food and Drug Administration (FDA) and European Medicines Agency (EMA), the MHRA have issued a press release on the [use of codeine in children](#). The key points from this press release are:

- 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 paediatric practice including 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 clinicians with a dilemma to either continue using 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.

At the heart of the problem is a series of recently recorded deaths from respiratory arrest in children and adolescents after adenoidectomy or tonsillectomy surgery given codeine after discharge from hospital. The doses used were within published prescribing limits and the deaths occurred after more than one day post-discharge. Associated factors appeared to be alteration in respiratory drive associated with obstructive sleep apnoea and variation in the metabolism of codeine for different genetic groups. Of particular concern is the significance of 'ultra fast metabolisers' who rapidly metabolise codeine to morphine through a genetic variant of cytochrome P450 CYP2D6. This variant is present in up to 0.7% of the general population but up to 30% of children of Middle Eastern and African/Ethiopian descent.¹ The metabolism to morphine can be accelerated in these individuals leading to increased effects and side effects. However, the role of the parent drug (codeine itself) and other metabolites remains unclear and there are other genetic variations of CYP2D6 that result in minimal conversion to morphine and therefore result in limited or no analgesia. Inadequate dosing of opioids results in avoidable pain while excess dosing risks adverse events that include respiratory



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depression or even respiratory arrest. All currently used opioids including codeine can be associated with ventilatory depression and all opioids can be highly variable in their clinical effects due to individual variation in both pharmacokinetic and pharmacodynamic factors.

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 safely and effectively. The decisions have been based largely on personal and institutional experience of different drugs, the availability of appropriate formulations of alternative drugs, and local hospital attitudes to the MHRA communication. There are many drugs which are used 'off licence' in paediatrics and there are some drugs that are used with caution by clinicians despite being contraindicated 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 NSAIDs are insufficient. Furthermore while codeine is contraindicated in all children who suffer from sleep apnoea after tonsillectomy/adenotonsillectomy, it is unclear if other opioids provide any greater margin of safety in this context. Nevertheless, children who have tonsillectomy, adenotonsillectomy, orchidopexy and some other procedures on a day stay basis commonly experience pain after discharge that is not effectively managed with the simpler analgesics.²

Additional information should be sought when considering the suitability of opioids for acute pain outside the hospital setting. A history of prior experience with codeine should be explored, 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 the child's response to the drug. For example, children who demonstrate an excessive response to opioid drugs during the perioperative period in terms of ventilatory depression or who are noted to have an unusual degree of sedation, reduction in ventilatory rate or even partial respiratory obstruction (snoring) after surgery may have increased susceptibility to these drugs. This should influence the choice and dosage of opioid drugs to be given after discharge from hospital. However, problems can arise even after uneventful overnight stays with the use of reduced doses oral codeine.³ In any event, the dose of any opioid should be adjusted in children with obstructive sleep apnoea and the response monitored in hospital prior to discharge.⁴

Different specialist paediatric hospitals have approached the problem of acute pain according to the collective experience of all those involved in care of the child, particularly the pharmacists who can advise on feasibility and formulation of available opioid drugs. We would recommend that paediatricians, anaesthetists and surgeons who are not practicing in a specialised paediatric centre may find discussion with their regional centre beneficial and supportive. The expertise may be useful in implementing a regional





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networked approach that can be monitored for efficacy and safety, while new evidence based guidance is obtained. It is essential that parents and carers receive education on the correct use of any opioid that they may need to use once their child is discharged from hospital. This should include both face to face guidance and written instructions regarding formulation, dose and frequency of administration, in addition to unambiguous dispensed drug labelling, that matches the written instructions.

WHAT ARE THE ALTERNATIVES? ■ ■ ■

Oral morphine, dihydrocodeine, tramadol and oxycodone are potential alternatives to codeine. Dihydrocodeine is unlicensed below the age of four years. 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 (see BNFC). As opioids are prescription only medications, these drugs need to be given to parents for their child in the form of a discharge pack or via a prescription which they can obtain from a pharmacy. Additionally, high strength morphine (100mg/5ml and tablets) and oxycodone are controlled drugs and tramadol is likely to become a controlled drug in the future, making prescription for home use more complex. The low concentration formulation of morphine (10mg/5ml) is not a fully regulated controlled drug although many hospitals regulate it in the same way as all other morphine preparations.

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. The current dosing guideline (2–12 years) for oral morphine is 200–300micrograms/kg every four hours according to response (see BNFC). A distinction needs to be made between analgesia used within the hospital and prescribed drugs for parents to administer after discharge, for moderate pain. In the hospital setting, with greater control and monitoring, it is usually possible to use higher doses safely. Most practitioners prescribing morphine outside the hospital setting as rescue analgesia are limiting each dose to less than 200 mcg/kg (usually 100mcg/kg) and are only providing a limited number of doses.

Some hospitals are moving to dispensing take home drugs that are not relabelled with specific physician based prescriptions. This is often the case with paracetamol and ibuprofen oral suspensions. The packaging will then simply have the standard dosing information based on age rather than weight. These instructions often use wide dose bands that do not take into account weight and lean body mass. This standardised approach when taken as directed carries a risk of suboptimal analgesia in some children and potential overdose in others which could lead to toxicity if used for extended periods of time.



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Commonly adopted approaches to opioid analgesia at present appear to be:

CODEINE ■ ■ ■

Continuing to use codeine outside the hospital setting with a strict dosing regimen for home use in the event of breakthrough pain. As part of routine anaesthetic surveillance, responses to opioids are observed carefully within the hospital setting leading to informed decisions on dosing regimens for opioid use outside the hospital setting (as described above). In children with known obstructive sleep apnoea having tonsillectomy, codeine is now contraindicated. However, few children have had formal sleep studies to provide irrefutable evidence of obstructive sleep apnoea. Therefore the surgical and anaesthetic teams need to assess each patient on an individual basis if they are considering the use of any opioids outside the hospital setting. Clearly children who have severe post-operative pain that necessitates opioid medication must be given effective analgesia that is safe regardless of their environment. In the extreme case of proven or symptomatic sleep apnoea, children may have to stay in hospital for longer if analgesia cannot be controlled with paracetamol and NSAIDs alone.

ORAL MORPHINE PREPARATIONS ■ ■ ■

Changing to the prescription of low dose morphine for breakthrough pain at home using doses described above. Some teams are uncomfortable with providing morphine outside the hospital setting albeit at a low-dose, even though it is not a controlled substance in this dilute formulation. However, as a precaution some groups are providing the appropriate amount of morphine as a limited number of individualised doses, with access to advice should pain continue. As with codeine, patients who have undergone removal of adenoids or tonsils with a history of obstructive sleep apnoea are a special case. Again, these patients need in-hospital evaluation of opioid sensitivity. Decisions need to be made whether to keep these children in the hospital until they no longer require opioids or to send them home with an appropriately considered dose of opioid for breakthrough pain.

DIHYDROCODEINE ■ ■ ■

Switching to the use of dihydrocodeine, which is licensed down to four years, and has dosing in the BNFC down to one year of age. The liquid formulation does contain some alcohol making it not ideal for children under one year.





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The advantage is that dosing of dihydrocodeine can be the same as that of codeine with the license covering most ages. The issue could be that there is no real advantage of dihydrocodeine in terms of safety over that of codeine as the metabolic pathway and mechanisms of analgesia are complex.⁵ For those who are currently thinking of continuing to use codeine there would be an argument to move to using dihydrocodeine so as to have the advantage of the regulatory cover provided by the existing product license in most children.

TRAMADOL ■ ■ ■

Providing tramadol in formulations and doses that are safe and child friendly. However, this is made more difficult due to the lack of available and appropriate formulations in the UK at present. The BNFC does not provide any dosing information on tramadol in children under 12 years of age and it is unlicensed below 12 years in the UK. However, it is widely used in Europe for younger children. Available formulations in the UK are capsules and soluble tablets containing 50mg of tramadol and oral tramadol drops of 100mg/ml (imported). Some groups are providing instructions on dissolving tablets and then providing a number of individual and individualised doses. While tramadol is regarded as having a reduced effect on respiratory drive compared to high efficacy opioids, its safety profile in children with a history of sleep apnoea after removal of tonsils or adenoids remains unproven. Tramadol also uses the same metabolic pathway as codeine and studies in ultra-fast metabolisers are still required to establish how genetic variance affects drug effect.

REFERENCES ■ ■ ■

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