Is there a role for codeine in paediatric anaesthetic practice?

In the UK until 2013 codeine was a weak opioid widely used for postoperative pain relief for children undergoing day case surgery. However, prescription of codeine in paediatric anaesthetic practice has changed dramatically since a Medicine and Healthcare products Regulatory Agency (2013) drug safety update.

Current Medicine and Healthcare products Regulatory Agency advice states that codeine should not be used in children (under the age of 18 years) who undergo tonsil or adenoid surgery for obstructive sleep apnoea. It also states that codeine should only be used to treat children over 12 years of age. The Association of Paediatric Anaesthetists of Great Britain and Ireland advocates this advice.

Because current advice does not contraindicate the use of codeine in all children, clinicians face a dilemma about whether to continue to use the drug with increased caution, or to use alternative analgesic agents.

Codeine can be used in children

Codeine has been a widely used and effective analgesic for many years. A Cochrane review by Moore et al (1998) demonstrated that, in combination with paracetamol, codeine is an extremely effective analgesic agent. It remains a valuable alternative for children who are intolerant of non-steroidal anti-inflammatory drugs. Additionally it avoids the need for use of controlled drugs and their associated regulatory constraints.

Tremlett (2013) highlighted that fatalities have been recorded in the USA and none have been reported in Europe. Reasons for this remain unclear but in the UK codeine is often prescribed as an as-required adjunct medication for home use whereas in the USA it is prescribed as a regular medication.

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All the potential alternatives to codeine have issues in these patients. Dihydrocodeine is unlicensed for use in patients below the age of 4 years. Tramadol is unlicensed for children under 12 years of age in the UK, and it also uses the same CYP2D6 pathway as codeine, making its metabolism unpredictable. Oxycodone is unlicensed in all children although doses are described for pain in palliative care. Oral morphine is a controlled drug and tramadol is already a controlled drug in some hospitals. This makes administration and prescription for home use more complex.

There is little evidence that these alternative opioids are safer than codeine. Tremlett et al (2010) suggested that, until sufficient evidence is available that other agents are as or more effective without unintended consequences for either the patient or other household members, use of codeine is likely to continue in patients without obstructive sleep apnoea.

Codeine should not be used in children

Codeine is a prodrug of morphine whose pharmacokinetics have not yet been fully elucidated. Around 5–15% of codeine is converted to morphine in the liver by the CYP2D6 enzyme. Genetic heterogeneity in this enzyme results in patients being classified as poor, intermediate and extensive metabolizers. In some individuals gene duplication results in three or more CYP2D6 genes being present, resulting in phenotypically increased functional enzyme activity. The frequency of such ultra-rapid metabolizers varies greatly with ethnic background.

The fatalities reported after codeine administration and resulting in the new Medicine and Healthcare products Regulatory Agency guidance occurred in ultra-rapid metabolizers receiving codeine. This resulted in high levels of morphine in the blood causing toxic effects such as respiratory depression.

The efficacy of codeine as an analgesic agent has also been questioned, as poor metabolizers receive little or no analgesic benefit from codeine administration. Tremlett et al (2010) asked why not simply use morphine? Its pharmacokinetics are understood, it is cheaper and it has well-documented protocols for multiple routes of administration.

The lack of availability of routine pharmacogenomic genotype testing for children makes accurate risk stratification difficult. Limited available paediatric formulations and difficulties associated with different routes of administration add further weight to the suggestion that a more suitable alternative should be sought.

Conclusions

The ban on prescribing codeine in children with obstructive sleep apnoea having adenotonsillectomy has a rationale; however, problems in a very small group of patients may have lead to unwarranted caution in wider prescribing. Thoughtful and selective use of this drug would allow it to remain a valuable part of a multimodal approach to postoperative analgesia. BJHM

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