**The restrictions to the use of codeine and dilemmas about safe alternatives.**

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 The effective management of children’s postoperative pain requires high quality pain assessment as well as appropriate pharmacological and non-pharmacological interventions. This requires that:

“postoperative analgesia should be appropriate to developmental age, surgical procedure, and clinical setting to provide safe, sufficiently potent, and flexible pain relief with a low incidence of side effects (APA, 2012 p33)

Pain management of children in the perioperative period is complex and remains sub-optimal with a high incidence of children experiencing moderate to severe perioperative pain (Russell et al 2013). This is partially due to misunderstandings about how children experience pain but may be further complicated by the frequent use of off label and unlicensed medicines in paediatric settings and the availability of age appropriate formulations (WHO 2012; Salunke and Tuleu 2013)

Codeine has been a popular postoperative analgesic in paediatric populations (Russell et al 2013) and was generally perceived to be ‘safe’ relative to other analgesics. Wynn-Jones et al.’s snap shot study of staff working in two district general hospitals examined staff views (59 doctors, 25 nurses) on the safety profile of codeine in paediatrics compared to other commonly prescribed analgesics. Of these 100% reported they would be more worried about morphine causing respiratory depression whereas only 42% has similar concerns about codeine. Codeine was also ranked as being safer than morphine (92%) and tramadol (82%) and ibuprofen (15%) . It is possible that similar (mis)perceptions may be held by parents.

However, in July 2013, the Medicines and Healthcare Products Regulatory Agency (MHRA) restricted the use of codeine in children in the UK following a review by the European Medicines Agency’s Pharmacovigilance Risk Assessment Committee (MHRA 2013). Previously, codeine was used as an oral analgesic agent in paediatric settings, usually in situations (e.g., postoperatively) where simple analgesia such as paracetamol and ibuprofen are not sufficient to relieve the pain. The review was prompted by the publication of case reports of death and severe respiratory depression in post-operative children following tonsillectomy or adenoidectomy (Ciszkowski et al. 2009; Kelly et al. 2012). The summary of the MHRA updated guidance issued by the MHRA in June 2013 states:

* Codeine should not be prescribed for children less than 12 years
* Codeine is contraindicated in those less than 18 years with obstructive sleep apnoea who have either tonsillectomy or adenoidectomy.
* Codeine is not recommended for use in children whose breathing might be compromised.
* Where codeine is prescribed for children 12-18yrs, the maximum daily dose should not exceed 240mg.
* Codeine should not be taken by breastfeeding mothers as the medicine can pass through breast milk to the baby.
* Codeine is contraindicated in all patients of any age known to be CYP2D6 ultra-rapid metabolisers

Codeine is not a great analgesic agent. It is a pro-drug requiring conversion by cytochrome P450 2D6 (CYP2D6) to morphine. This enzyme is subject to genetic variation. In the Caucasian population, approximately 7% are CYP2D6 poor metabolisers, and so will not convert much codeine to morphine, and will derive little analgesic effect. Conversely, approximately 5% of Caucasians (but up to 30% Ethiopians) are ultra-rapid metabolisers, meaning there is greater conversion to morphine, and with increased risk of adverse effects including respiratory depression (Bradford 2012)

While it is undoubtedly true that one preventable death in any area of medicine, but especially paediatrics, is one too many, this decision by the MHRA leaves clinicians with a problem. Is there evidence that the alternatives to codeine are safer? Which alternative is most efficacious? Options for clinicians include morphine, dihyrdrocodeine or tramadol, but each should be approached with caution. There is little to no relative safety or efficacy evidence between any of them, or even to show improved safety profiles compared to codeine. Specific issues for children also include the limited child friendly formulations of the alternatives (especially tramadol).

Historically, research into children’s medicines has lagged behind those used in adults due to ethical concerns about involving children in clinical trials and the pharmaceutical industry’s reluctance to invest in specific markets. Recent policy changes have stimulated research into paediatric medicines (European Union 2006; Salunke and Tuleu 2013) but significant gaps in the knowledge of paediatric analgesics remain. Restricting the use of codeine in paediatrics may have been done for the right reasons, but until the evidence gap left behind is filled, the safety and efficacy of oral analgesia given to children with pain remains unknown.

Codeine looks set to disappear from paediatric formularies and monitoring the use of alternative analgesics used in paediatric settings has now gained greater urgency. As Tremlett (2013 p682) notes, there is need to *“actively encourage the reporting of the effectiveness and safety of alternative agents to manage break-through pain in children on multimodal analgesic”.* Reporting all suspected adverse drug reactions in children from oral analgesics to pharmacovigilance regulatory authorities, such as the MHRA ‘s Yellow Card Scheme (MHRA 2013) will be an important step in the right direction.

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