Codeine phosphate in children: time for re-evaluation?

Codeine is a well-established drug in the pain armamentarium. It is classed as a ‘weak opioid’ and used to treat pain of mild to moderate severity, either alone or in conjunction with non-opioids. Its route of administration is usually oral or intramuscular (i.m.), although there is a growing interest in using the rectal route in children, from where it is rapidly absorbed, achieving a peak plasma concentration in 30–60 min. In this recent study, a dose of codeine 1 mg kg⁻¹ given either rectally or i.m. in children over 3 months old produced a peak codeine level at 30 min, but with a consistently lower plasma level when given rectally. The lower plasma level after rectal administration reflects the reduced bioavailability of the drug when given by the rectal route.

Codeine or methylmorphine is an opium alkaloid about one-tenth as potent as morphine. Its use is advocated in the management of acute and chronic pain. It is cited extensively in World Health Organisation (WHO) literature, being part of the WHO essential drugs list, for the management of pain from cancer and AIDS. It is commonly used to manage pain after adenotonsillectomy, dental extraction and neurosurgery in adults and children.

In the 1990s, the advent of Acute Pain Services brought a more organized management of pain in children. As part of this phenomenon there has been a change in practice from using mainly morphine and paracetamol for pain control, to
Pharmacogenetic testing is currently used in only a limited way from having a pharmacogenetic DNA chip for use control or as a cough suppressant in children over 1 yr old, such as codeine, warfarin and amitriptyline among others. Despite codeine being an ‘old’ drug, there are few clinical studies in children which relate blood levels of codeine or morphine to pain score. When pharmacokinetic studies are done, they rarely involve all paediatric age groups—from neonate to adolescent. We often depend on data from older patients to guide us in our dosing strategies. Is there any evidence in adults that codeine can provide good analgesia?

The last 10 yr has seen the use of systematic review to evaluate different analgesic drugs. Combined data from multiple randomized controlled trials can be used to estimate the effectiveness of a drug or intervention with more validity than any single trial permits. A statistical concept, which is useful in measuring effectiveness is the number needed to treat (NNT) to produce a specified outcome. For an ideal analgesic this would be 1. The Oxford League Table of Analgesic Efficacy ranks drugs in order of NNT to produce 50% pain relief for 4–6 h in patients with moderate to severe pain. Codeine 60 mg has a NNT of 17, and comes at the bottom of the table. Paracetamol 1000 mg has a NNT of 4.6 and paracetamol 1000 mg with codeine 60 mg a NNT of 1.9, illustrating the additive effect of combining the two drugs. The only drugs which score higher are the NSAIDs, particularly ibuprofen and diclofenac. Only ibuprofen is licensed for use in children to treat acute pain.

Just as in adults, NSAIDs can be contraindicated in children because of renal dysfunction, bleeding or gastrointestinal upset. Sometimes we need a drug to manage a moderate degree of pain other than paracetamol. Some would say that we should use morphine—this may be like taking a hammer to crack a nut for some situations. Maybe before discarding codeine as a poor analgesic we should utilize the information gleaned from systematic reviews and use codeine in combination with paracetamol for managing moderate pain. The commercially available combined preparations may not always fit the bill when giving drugs on a weight basis (Table 1). Only Co-codamol 8/500 is licensed for use in children. Combined preparations remain non-user friendly for children; the low dose preparation contains too little codeine and the others are difficult to subdivide to give adequate doses of both drugs to all sizes of children. However, even without a suitable combined preparation for use in children, there is no reason why these drugs cannot be given in tandem to optimize their effectiveness.

In the meantime, drug research in children needs to be much more structured. Drugs need to be systematically assessed for effectiveness in all age ranges, from premature infants to adolescents, even drugs that have been available for many years. There is a general disapproval of giving drugs by the i.m. route to children and the rectal route is an increasingly attractive alternative especially in younger children. We need to know more about the pharmacokinetics of drugs depending on the route of administration.

### Table 1

<table>
<thead>
<tr>
<th>Codeine dose (mg)</th>
<th>Paracetamol dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-codamol 8/500</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>500</td>
</tr>
<tr>
<td>Co-codamol 30/500</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>500</td>
</tr>
<tr>
<td>Co-codamol 60/1000</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>1000</td>
</tr>
</tbody>
</table>

In this issue, Williams and colleagues review the evidence concerning codeine’s analgesic efficacy and call it into question. Some studies have shown codeine to have a variable effect. Codeine has been extensively used to provide analgesia following craniotomy, but a series of articles by Stoneham and Walters demonstrate inadequate analgesia with codeine in adults and recommend the use of patient controlled analgesia (PCA) with morphine as a better alternative.

Following absorption, codeine undergoes extensive metabolism, with 5–15% undergoing O-demethylation with CYP2D6, a cytochrome P450 enzyme, to form morphine. It has been put forward that it is only this portion of the drug which produces analgesia, although some believe that codeine has a small inherent analgesic action. The variable effect of codeine is a result of genetic polymorphism. The cytochrome P450s are a multigene family of enzymes. The level of expression or function of these enzymes has a major effect on drug efficacy. Patients in whom the cytochrome P450 gene encoding contains inactivating mutations are ‘poor metabolizers’ (PMs), and have a severely compromised ability to metabolise drugs such as codeine, warfarin and amitriptyline among others. Pharmacogenetic testing is currently used in only a limited number of specialist centres around the world. We are still a long way from having a pharmacogenetic DNA chip for use at the bedside or in clinic to determine a patient’s drug sensitivity.

So is it time to re-evaluate our use of codeine? Is there enough evidence for us to throw it in the bin? Drug research in children always lags significantly behind that in adults. Many pharmaceutical companies do not pursue a product license for their drugs to be used in children, because of cost. Codeine has a license to be used for pain control or as a cough suppressant in children over 1 yr old, given by the oral or i.m. route. It is not licensed for use rectally. Despite codeine being an ‘old’ drug, there are few clinical studies in children which relate blood levels of codeine or morphine to pain score. When pharmacokinetic studies are done, they rarely involve all paediatric age groups—from neonate to adolescent. We often depend on data from older patients to guide us in our dosing strategies. Is there any evidence in adults that codeine can provide good analgesia?
and the effects that age and organ maturity have on drug behaviour. Pain assessment is difficult in preverbal children, but it is possible to perform with time and effort. We need more studies which relate pain score to therapeutic blood levels of drugs in children. It may still be a little early to throw out codeine, particularly when we have few drugs adequately investigated with which to replace it.

M. Cunliffe
Department of Anaesthesia
Royal Liverpool Children’s NHS Trust
Liverpool L12 2AP
UK

References
15 Stoneham MD, Cooper R, Quiney NF, Walters FJ. Pain following craniotomy: a preliminary study comparing PCA morphine with intramuscular codeine phosphate. Anaesthesia 1996; 51: 1176–8
20 The Oxford Pain Internet Site July 1999. www.jr2.ox.ac.uk/Bandolier/painres/painpag/index