Codeine phosphate in paediatric medicine

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Codeine is an old drug that still enjoys widespread clinical use although the logical basis for its popularity has been questioned.66 It is considered to be suitable for mild to moderate pain but not for more intense pain even in large doses.94 The World Health Organisation has devised a three-step analgesic ladder for the progressive treatment of increasing pain; on this codeine is considered a weak opioid and occupies a position on the second step (Fig. 1).113 A significant degree of unpredictable, variable or poor response to treatment with codeine has been reported in many human and animal studies. Indeed, some single dose studies in adults, have shown no difference between codeine and placebo,54 60 and a quantitative systemic review suggests that codeine 60 mg has a number needed to treat (NNT) of 18 which is very high when compared with 5.0 for paracetamol 600 mg and 3.1 for the combination.78 Codeine is frequently recommended for paediatric use.2 37 100 A recent survey of paediatric anaesthetists in the UK showed that alongside morphine and fentanyl, codeine is the most widely prescribed opioid analgesic in paediatric anaesthetic practice.34 The reputedly lower incidence of opioid-related side effects has made codeine popular for the younger age groups including neonates and especially in situations where airway management and neurological assessment are critical.56 69 102 106 These suggested benefits have been noted after single doses although they may not exist when repeated doses are used.69 In fact, few clinical studies of the analgesic efficacy or side effects of codeine in children have been undertaken, and although the incidence of side effects may be low, analgesia may be inadequate for post-operative pain in some circumstances.102 Pain assessment is difficult in paediatric populations especially neonates and preverbal children and this complicates both the study and use of analgesics particularly those with low efficacy or unpredictable effects. Significant variability in both the pharmacokinetics and pharmacodynamics of codeine has been shown in animal and adult human laboratory experimental studies.24 25 38 74 105 112 115

In this review we shall examine the reasons for this variability and unpredictability in the effects of codeine in both laboratory and clinical investigations and assess evidence for its suitability for use in preverbal infants and children.

Pharmacology of codeine37 40

Codeine (Fig. 2) is a naturally occurring opium alkaloid: 7,8-didehydro-4,5-epoxy-3-methoxy-17-methyl-morphinan-6-ol monohydrate.¹ Like morphine it is a constituent of the opium poppy, Papaver somniferum. It was isolated from opium in 1833 by Robiquet and its pain-relieving effects were recognized shortly after. Codeine constitutes about 0.5% of opium, which continues to be a useful source of its production, although the bulk of codeine used medicinally is prepared by the methylation of morphine. Codeine is less potent than morphine, with a potency ratio of 1:10.111

Dosage and uses

Codeine can be given by the oral, rectal and intramuscular (i.m.) routes. The intravenous (i.v.) route is not recommended because of dangerous hypotensive effects probably
related to histamine release. In children, it is generally given in doses of 1 mg kg$^{-1}$ up to a maximum of 3 mg kg$^{-1}$ day$^{-1}$; however, larger doses have been used. Codeine is often used in combination with other drugs, for example aspirin, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and diphenhydramine in the treatment of mild to moderate pain. In neonates and children it has been used in both acute and chronic painful conditions and particularly for post-operative and cancer pain. Its antitussive and constipating properties also mean that it is used in many cough, cold and antidiarrhoal remedies.

**Pharmacokinetics**

The vast majority of pharmacokinetic data for codeine has been obtained from investigations in adults. Very little information is available from studies in children or infants and to our knowledge there is no published work in neonates.

Codeine is rapidly, and well absorbed following oral administration, approximately 50% undergoing pre-systemic metabolism in the gut and liver. Peak plasma concentration occurs after approximately 1 h and the plasma half-life is 3–3.5 h. Absorption is faster after i.m. injection, the time to peak plasma concentration is about 0.5 h. The volume of distribution is 3.6 litre kg$^{-1}$ and the clearance is 0.85 litre min$^{-1}$. Rectal codeine has been recently introduced into paediatric practice. A study in healthy adult volunteers showed no difference in codeine bioavailability following rectal or oral administration with a systemic availability of about 90%. In the post-operative period these values may be less predictable; in one study clearance varied 4-fold and systemic availability after oral dosage was between 12 and 84%.

Available research findings imply that age specific differences in the pharmacokinetics of codeine may be significant. In a comparison of i.m. and rectal codeine in children aged 3 months to 12 yr for post-operative analgesia, peak plasma levels of codeine were achieved as expected between 30 and 60 min in both groups but rectal bioavailability was found to be lower. In another study of rectal codeine for post-operative analgesia in infants and children aged between 6 months and 4 yr, the mean initial half-life was 2.6 h, but in the infants of the lowest body weight, the half-life was over 2 h longer than this mean value. In addition, plasma drug concentration data indicate that a rectal dose of codeine of 0.5 mg kg$^{-1}$ in children can result in similar, or slightly greater, plasma concentrations of codeine and its metabolites than after 60 mg orally in adults. More information is clearly required, particularly for neonates and in the post-operative setting in order to understand fully the effects of development on codeine pharmacokinetics in clinical situations.

**Metabolism**

Codeine is principally metabolized in the liver in one of three ways: glucuronidation at the 6-OH position, the principal route; N-demethylation to norcodeine (10–20%); and O-demethylation to morphine (5–15%). Between 5 and 15% of the drug is excreted unchanged in the urine (Fig. 3). Other minor metabolites, normorphine and hydrocodone, have also been identified.

In 1948, Sanfilippo first suggested that the analgesic effect of codeine was because of the proportion of the drug metabolized to morphine and this has lead to the belief that codeine is a prodrug, with morphine as its principal active metabolite and having little or no intrinsic analgesic activity of its own. The efficacy of a prodrug is dependent on the amount of active metabolite formed. Variable expression of the enzymes involved in the biotransformation of drugs can lead to substantial differences in the production rate and plasma concentration of metabolites, and hence, the efficacy of a prodrug.

It has been known for some time that genetic variability in drug metabolism is an important cause of inter-individual variations in drug efficacy and maturation of enzyme systems is another important factor for certain compounds. O-Demethylation of codeine to morphine is dependent on the cytochrome P450 enzyme, CYP2D6, which is known to show genetic polymorphism, whereas the other metabolic pathways for codeine are not dependent on this enzyme. N-Demethylation for example is catalysed by CYP3A, another P450 enzyme.

A large number of different genetic variants are known to exist for CYP2D6, which leads to a wide spectrum of metabolic capabilities within study populations.
discussing these differences, individuals are normally classified as either poor metabolizers (PM) or extensive metabolizers (EM) depending on the activity of the enzyme, although this is known to be an oversimplification (see below). Poor metabolizers will produce little or no morphine from codeine whereas extensive metabolizers will produce significant amounts of morphine although the actual amount produced may show wide variation. The metabolic differences between PMs and EMs are known to remain constant even after chronic codeine dosing.

Despite the popularity of codeine in paediatric practice, the influence of development on the efficacy and side effects of codeine has not been well investigated. It has been suggested that infants and neonates have a reduced metabolic capacity for codeine. CYP2D6 activity is absent or less than 1% of adult values in fetal liver microsomes. Demethylation of codeine to morphine does not occur in utero but activity of the enzyme is known to increase markedly immediately after birth regardless of gestational age. This increase in enzyme activity is maintained, although it may still be below 25% of adult values before 5 yr old. The efficiency of the enzyme to carry out the O-demethylation reaction also appears to be much lower in neonates than in adults. The glucuronidation pathway is also immature at birth and it has been shown that it continues to develop after the neonatal period. In contrast, N-demethylation has been found to be equivalent to that in adults at all pre- and post-natal ages.

CYP2D6 has approximately 60 unique P450 genes, although only half a dozen, including CYP2D6, are responsible for the metabolism of the vast majority of the ‘over the counter’ and prescribed drugs. CYP2D6 is usually considered to be a hepatic enzyme but it is probably present in other organs and tissues, and has been identified in rat and canine brain tissue. It has also been identified in human brain preparations.

Unlike the majority of the other P450 genes CYP2D6 is not inducible, although there is growing evidence associating the enzyme with a number of disease states. Enhanced activity has been associated with malignancies of the bladder, liver, pharynx, stomach and, particularly, cigarette smoking related lung cancer. There has also been a link with chronic inflammatory diseases, such as rheumatoid arthritis and ankylosing spondylitis, and neurodegenerative disorders. Enhanced CYP2D6 mediated metabolism of one or more dietary/environmental agents may form a reactive intermediate that plays a role in cancer initiation and/or promotion in various tissues. Reduced enzyme activity is thought to be associated with an increased risk of Parkinson disease.

CYP2D6 polymorphism is responsible for variation in spartine/debrisoquine oxidation. This particular oxidative step is important in the metabolism of more than 30 drugs and environmental chemicals, including about 20% of commonly prescribed drugs, for example tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), some neuroleptics, some antiarrhythmics and ß-adrenoceptor blockers as well as codeine and tramadol.

The gene subfamily has been mapped to chromosome 22 at 22q13.1 and shows autosomal recessive inheritance. CYP2D6 activity ranges from complete deficiency to ultrafast metabolism, depending on which genetic variant is present. To date, 55 variants have been identified and classified. Most are rare with 87% of genotypes being accounted for by five different variants in the populations studied. Classification of individuals as PMs or EMs

\[ \text{CYP2D6} \]
correlates with the genetic variant expressed and the presence of activity altering mutations in the gene. This is done by either phenotyping, using sparteine, debrisoquine or dextromethorphan as the probe drug, or by genotyping, using DNA extracted from leucocytes for a polymerase chain reaction (PCR) DNA test.

Misclassification can occur in the presence of drugs that are inhibitors of CYP2D6, for example quinidine, metoclopramide, some neuroleptics, some SSRIs and some antiarrhythmics. This is commonly because of the competitive inhibition of codeine metabolism as it has a relatively low affinity for the enzyme compared with these other compounds.

The estimated frequency of PMs in the UK is about 9%. However, there is wide variation among ethnic groups, from about 1% in Arabs to 30% in Hong Kong Chinese. Caucasians have an incidence of about 7%. The frequency of ultra-rapid EMs, a subgroup of EMs who are able to metabolize CYP2D6 substrates relatively quickly, also shows ethnic variation from 29% in Ethiopia to 1% in Swedish, German and Chinese populations. In addition, variability occurs within genotypes; studies comparing Chinese and Caucasian EMs have shown differences in the pharmacokinetics of codeine. This has been confirmed in investigations of other population genotypes.

Pharmacodynamics

Mechanism of action

Potentially codeine could act via a number of different mechanisms. It may have a direct (opioid or non-opioid receptor mediated) analgesic effect or, as already mentioned, may act through metabolism to morphine or other active metabolites. Codeine binds to the μ receptor like morphine but with a much lower affinity. It also binds to the κ and δ receptors but again has a much lower affinity than morphine, though the difference is less marked. The affinities of the metabolites codeine-6-glucuronide and norcodeine to the μ receptor are similarly low. Early animal studies produced conflicting results; morphine tolerant mice were found to be less tolerant of codeine and the analgesic effect of codeine is less easily reversed by naloxone than that of morphine. Although, in a rat model significant analgesia was demonstrated only in those animals able to metabolize codeine to morphine.

Further attempts to elucidate the mechanism of action of codeine used adult human experimental models to compare the effect of codeine on phasic and tonic pain. Phasic pain is a result of a stimulus of varying intensity, analogous to pain with movement, which is known to respond poorly to opioids. Tonic pain is a result of a constant intensity stimulus and is analogous to rest pain and is opioid sensitive.

Codeine was shown to have no effect on opioid-insensitive phasic pain in either extensive or poor metabolizers in these studies, which suggests that an opioid receptor mediated effect for codeine is likely. Results from this study also showed that EMs but not PMs, had a good response for tonic pain, suggesting that in man codeine analgesia is both an opioid effect and that the formation of morphine is an important factor. Confirmatory evidence for the dominant role of morphine in the effects of codeine in man have been obtained by competitive inhibition of codeine O-demethylation using quinidine. The results from these studies show that codeine analgesia in extensive metabolizers could be blocked by pretreatment with quinidine. Studies in (adult human) volunteers using the same technique have shown that the incidence and magnitude of respiratory, pupillary and psychomotor effects are also dependent on codeine metabolism to morphine.

Recently no analgesia from codeine was demonstrated in PM groups, even at high doses. However in EM groups in these studies, analgesia was found to be slightly greater following codeine than with a dose of morphine producing similar plasma levels of morphine. Although this work provides strong evidence for the dominant role of morphine in codeine analgesia, the slightly increased efficacy of codeine at similar plasma levels of morphine must be explained.

It is possible that other metabolites are responsible; there may be a pharmacokinetic mechanism or there may be a small direct analgesic effect of codeine itself. A recent study using a rat animal model has shown that hydrocodone, a possible minor codeine metabolite, has analgesic properties that are independent of its O-demethylated metabolite hydromorphone. However, the lack of analgesic effect consistently seen in poor metabolizers makes both this mechanism and a direct effect of codeine itself unlikely.

Another explanation may be that the rapid penetration of the blood–brain barrier (BBB) by codeine and expression of CYP2D6 in the brain lead to higher levels of morphine in the central nervous system (CNS). Codeine is known to penetrate the BBB more rapidly than morphine, and the presence of CYP2D6 in the CNS allows local tissue O-demethylation of codeine to morphine. This has been shown to be possible in rat brain homogenates and the presence of CYP2D6 has been demonstrated in both human and animal brain tissue. Demonstration of a direct correlation between analgesia and plasma levels of morphine or its metabolites have proved to be elusive and studies difficult to interpret, particularly in children.

Clinical efficacy

Both adult and paediatric clinical studies have demonstrated that the efficacy of codeine is low and that it has a ceiling effect at higher doses above which there is a marked increase in the incidence of side-effects. Two recent systematic reviews have shown a small but
significant benefit of adding codeine 60 mg to paracetamol in adults.\textsuperscript{35,78} Many other studies, also in adults, confirm that codeine 30–60 mg can add significantly to the analgesic effect of drugs such as aspirin, paracetamol and NSAIDs.\textsuperscript{10,27,28,44,48,63,90} This additive effect is especially prominent after repeated doses, and accumulation of morphine has been suggested as an explanation.\textsuperscript{46,90}

Unfortunately, there have been very few clinical studies investigating the analgesic efficacy of codeine in which genetic variation is taken into consideration, and none in paediatric groups. In the only study of post-operative patients to consider this factor, the analgesic efficacy of codeine was found to be low but overall there was no difference in efficacy between the two phenotypes.\textsuperscript{88} However, the number of PMs was very small and the overall efficacy of codeine was low throughout the study. In addition, amongst the EMs there was a very wide spectrum of metabolic ability and patients with higher concentrations of morphine and morphine-6-glucuronide had a significantly better analgesic response. Interestingly, serum concentrations of morphine and its metabolites after 1 h were much lower in the EMs in this study than those that have been generally found in healthy EM volunteers.\textsuperscript{24,36,89,103,105,115} This suggests that post-operative factors may significantly influence codeine metabolism, possibly leading to lower plasma concentrations of morphine and its metabolites.

**Non-analgesic effects**

Codeine has a side-effect profile that is broadly similar to other opioids (Table 1).

One of the reasons codeine has maintained its popularity is a reputedly lower incidence of opioid-related side effects in comparison with other drugs from this group. Codeine is commonly used for post-operative analgesia following neurosurgery because of its supposed lack of sedation, respiratory depression and the preservation of pupillary signs. A recent survey of neuroanaesthetists suggested that codeine and dihydrocodeine were the mainstays of post-operative analgesia, but in 50% of cases the same anaesthetists considered this analgesia to be inadequate. Most said they would not use morphine as an alternative for fear of side effects.\textsuperscript{106} There is little evidence to confirm that the side effects of codeine are significantly fewer or less severe than those of other opioids at equi-analgesic doses. The antitussive and gastrointestinal effects of codeine have been found to occur at lower doses than those for analgesia, but the mechanism has not been fully elucidated.\textsuperscript{104} Studies of gastrointestinal transit time have been largely inconclusive although in the only study to measure post-codeine morphine levels, the transit time was longer in the group who also had significantly higher plasma morphine.\textsuperscript{49,50,75}

The extent to which the different non-analgesic and adverse effects of codeine can be attributed to metabolism to morphine is not known; there is increasing evidence, however, of a direct role for codeine itself. Single dose comparisons of codeine, morphine and placebo in adult volunteers have shown that at low doses side effects appear to be directly related to plasma morphine levels but that at higher doses codeine may itself be directly responsible for adverse effects.\textsuperscript{38,87} The importance of this finding is that, ironically, poor metabolizer groups whilst having inadequate analgesia may still experience side-effects from codeine.

Another group of patients that may experience enhanced adverse effects from codeine are the ultra-rapid extensive metabolizers. Recovery of the O-demethylated metabolites is much higher in the ultra-rapid EMs (15.3 vs 1.7–8.7% in EMs and 0.4% in PMs).\textsuperscript{114} Thus, ultra-rapid EMs may develop increased morphine dependent effects or side effects of codeine and in addition lower than normal doses may be necessary to achieve the required therapeutic effect.\textsuperscript{12,13} In an interesting case report, a 33-yr-old woman experienced the acute onset (less than 30 min) of colicky abdominal pain, euphoria and dizziness following codeine 60 mg after a tooth extraction.\textsuperscript{30} The same symptoms recurred following a second dose of 30 mg. She was later phenotyped and found to be an ultra-rapid EM. Rapid and extensive formation of morphine by O-demethylation of codeine was the suggested cause of these symptoms.

It has been suggested that a dose of codeine 1 mg kg\textsuperscript{-1} i.m. or orally in neonates and children is associated with a low risk of respiratory depression, although with repeated dosing this advantage may be lost.\textsuperscript{94} In fact, there are few data on the non-analgesic effects of codeine in children. Respiratory and pupillary effects in comparison with other opioids have not been specifically investigated.

Post-operative vomiting after adenotonsillectomy in children has been found to be significantly less after codeine in comparison with morphine for ‘equipotent’ doses in a recent study.\textsuperscript{102} Absence of or reduction in unpleasant or potentially dangerous side effects for equal analgesia in comparison with other opioids would be an important advantage for codeine. Unfortunately, the evidence for this is scant.

**Conclusion**

As the major proportion of the analgesic effect of codeine appears to be because of its metabolism to morphine, a large
inter-individual variation in efficacy is to be expected with at least 9% of the UK population having little or no benefit. In effect, codeine administration may be regarded as a complicated and unreliable way of giving a low dose of morphine. As long ago as 1964, Lasagna noted that ‘codeine possessed most of the disadvantages of morphine’ and that ‘its use could be avoided by using a dose of morphine less than 10 mg’.

Altered pharmacokinetic effects, particularly in the post-operative period, may also reduce its efficacy.

In early life, the immaturity of infant metabolic processes is also likely to reduce the efficacy of codeine. Furthermore, there is evidence that adverse effects may occur in the absence of analgesia in poor metabolizers of the drug. Genetic polymorphism may be an important factor responsible for the low efficacy of the drug in population studies and the high NNT in systematic reviews. It is interesting to note that during drug development those compounds subject to selective metabolism by polymorphic enzymes are often discarded in the early stages. If codeine had been discovered today it is possible that it would not have made it as far as the pharmacy shelves.

The development of efficient and inexpensive methods of genotyping for enzyme polymorphisms, transport proteins and drug receptors may enable genetic information to be used in the future to tailor drug therapy for each individual. However, until this type of screening is widely available, there is no way to accurately predict whether an individual patient will obtain a significant analgesic effect from a dose of codeine.

Overall there has been little clinical research into the use of codeine in children. From that which has been done it appears that the popularity of codeine in this patient group is not supported by convincing data of its efficacy or suitability, despite its apparently good safety record. The available evidence implies that codeine may in fact be particularly unsuitable for use in the younger child given the difficulties in pain reporting and assessment in this group and the unpredictable effects of the drug. In comparison with other opioids there is little evidence to support the commonly held view of a reduced incidence of serious side effects in the presence of equivalent analgesia. Further investigation in paediatric populations is required if its continued use is to be justified.

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