



# Cautions with codeine

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## Summary

**Codeine is a weak opioid analgesic. It has to be converted to morphine, but there is significant inter-individual variation in its pharmacokinetics which results in variable effectiveness. Codeine's efficacy in clinical trials is generally modest and while its adverse events are generally mild, serious adverse events, including death, have occurred. Tolerance and drug dependence can occur. There is a risk of toxicity especially if combination products containing codeine and other drugs are misused. Treatment with simple analgesics, or other opioids if required, provides a more predictable response.**

Key words: opioids, analgesia, pharmacogenetics, pharmacokinetics.

(Aust Prescr 2011;34:xx)

## Introduction

Codeine is a widely available analgesic in both prescription and over-the-counter preparations in Australia. It is often combined with paracetamol or a non-steroidal anti-inflammatory drug (NSAID). Codeine is generally perceived as a safe and effective analgesic, however there have been calls to withdraw codeine from the market.<sup>1</sup>

## Pharmacokinetics and pharmacogenetics

Codeine has low affinity and low intrinsic activity at the opioid receptor which is responsible for most of the analgesic effect. It therefore requires conversion to morphine by endogenous enzymes, principally cytochrome P450 2D6 (CYP2D6), to have an analgesic effect. There is significant inter-individual variability in the activity of this enzyme. These genetic variations affect the rate at which people convert the prodrug to morphine.

Slow metabolisers are unable to convert enough codeine to produce the morphine concentrations needed for an analgesic response. These patients may experience some of the adverse effects of codeine,<sup>2</sup> particularly if the dose is increased to try and improve the response. However, some adverse effects such as constipation may be mediated through morphine (similar in mechanism to the analgesic effect), suggesting that slow metabolisers are less prone to these effects.<sup>3</sup> Ultrafast metabolisers may be at risk of opioid toxicity, including life-threatening respiratory depression, because of the augmented metabolism of codeine to morphine. The prevalence

of both slow and ultrafast CYP2D6 metabolism in the population varies (approximately 2–20%), differing significantly with ethnic background (Table 1). While it is possible to screen for CYP2D6 polymorphisms prospectively (at least in some countries), this is unlikely to be a cost- or time-efficient strategy.

Drugs which inhibit CYP2D6, including many antidepressants such as paroxetine, sertraline and citalopram, may reduce the efficacy of codeine. Enzyme inducers, such as phenytoin, may augment the effect. In addition to the CYP2D6 variations, other genetic variants affecting morphine metabolism, blood–brain barrier transit and opioid receptor kinetics may also have significant effects on an individual's response to codeine.<sup>1</sup>

## Efficacy and place in therapy

The World Health Organization places codeine as a 'step 2' (weak opioid) on its pain ladder. Published in 1990, this was originally a guideline for the treatment of cancer pain, but has often been extrapolated to other painful conditions. Other organisations, however, have been much less convinced of the role of codeine in therapy. Therapeutic Guidelines: Analgesia states that codeine's 'place in therapy is uncertain' and highlights that it has a limited role in palliative care.<sup>2</sup>

There is great heterogeneity in the clinical trials involving codeine, with marked differences in patient enrolment, type of pain, dose of codeine and the comparative drugs used. In general, the efficacy of codeine in clinical trials is disappointing. In a meta-analysis, codeine, as a single drug for postoperative pain, did not provide adequate analgesia (defined as a 50% pain relief over 4–6 hours) in a large proportion of patients (response rate 26% for codeine 60 mg versus 17% for placebo). The response rate was worse in dental procedures than with other surgical procedures. Codeine performed unfavourably

Table 1

### Prevalence rates of CYP2D6 polymorphisms by ethnicity<sup>18</sup>

Ethnicity	Slow metabolisers	Ultra-fast metabolisers
Western European	8–10%	1–4%
Southern European		7–10%
African	0–20%	5–30%
Eastern Asian	0–1%	
Arabian		Up to 20%

compared with simple analgesics such as paracetamol and NSAIDs.<sup>4</sup> When combined with paracetamol, codeine appeared more clinically useful. However, the additional effect of codeine, compared with the same dose of paracetamol alone, was modest, with a further 10–15% of patients achieving adequate analgesia.<sup>5</sup> A meta-analysis of opioids for osteoarthritis of the knee or hip found that the modest benefits of codeine were outweighed by adverse events.<sup>6</sup>

Many of the preparations available in Australia contain less codeine than the doses studied in most clinical trials (generally 60 mg codeine). It is questionable if these low-dose codeine combination products (containing 8–15 mg codeine per tablet) provide meaningful analgesia over simple non-opioid analgesics alone.<sup>7</sup>

### **Adverse effects**

The common adverse effects of codeine, which include nausea, vomiting, constipation, drowsiness and dizziness, become more likely with higher or repeated doses. Constipation can be particularly problematic with larger doses and codeine is best avoided after bowel surgery. Medication overuse headaches are a concern in people using codeine-containing medications regularly (more than 10 days per month). While the risk of developing medication overuse headache with codeine is unknown (given multiple confounding factors in observational studies), combination analgesics and opioids (such as codeine) are likely to have a significantly higher risk than simple analgesics such as paracetamol or NSAIDs.<sup>8,9</sup> Less well appreciated, but seen in some epidemiological studies, is the small but significant risk of falls, fractures and even motor vehicle accidents.<sup>10–12</sup>

At higher doses, or in ultrafast metabolisers, life-threatening respiratory depression can occur especially when codeine is combined with other respiratory depressant drugs, such as benzodiazepines.

### **Breastfeeding**

Attention was raised to the potential harms of codeine during breastfeeding after the death of a neonate whose mother had been prescribed codeine postpartum. Very high concentrations of morphine in the deceased baby's blood were attributed to the mother being a CYP2D6 ultrafast metaboliser.<sup>13,14</sup> The US Food and Drug Administration issued a letter outlining the need for caution and close monitoring if prescribing codeine to breastfeeding women.<sup>14</sup> The Australian Medicines Handbook advises avoiding codeine in breastfeeding women.<sup>15</sup>

### **Children**

Due to their developing physiology and body composition, infants and young children have an increased susceptibility to the adverse effects of opioids. Pharmacogenetic variants were identified as a causal factor in the death and anoxic brain injury of two young children given codeine for analgesia after tonsillectomy. Several countries have set minimum ages for

codeine use, however the age they set varies considerably given the lack of clarity as to when the risk diminishes.<sup>1</sup> Some children's hospitals have removed codeine from their formularies.<sup>1</sup> The UK Medicines and Healthcare Products Regulatory Agency advises that codeine-containing preparations for cough should not be used by people less than 18 years old, as the risks outweigh the benefits.<sup>16</sup>

### **Elderly**

Older people have an increased susceptibility to opioids. They may also be taking interacting drugs. Pharmacogenetic variability can have a considerable impact on adverse effects such as sedation, confusion, falls and injury. While combination products containing codeine are often considered safe, a cohort study found the risk of injury was higher in older people using these products than in those taking other opioids or sedating drugs.<sup>12</sup>

### **Drug dependence and codeine abuse**

Although considered a weak opioid, codeine, like all opioids, is associated with the problems of tolerance and drug dependence with long-term use. Codeine abuse is also of concern particularly with combination products, as it frequently results in exposure to supratherapeutic doses of paracetamol or NSAIDs. Deaths and serious morbidity, such as liver toxicity and gastric haemorrhage, have been reported.<sup>17</sup>

Access to codeine within Australia is inconsistent. Codeine 30 mg tablets are classified 'schedule 8' (drugs with potential for abuse or addiction), whereas the same dose combined with paracetamol is classified 'schedule 4' (drugs available with prescription). A large number of lower-dose combination preparations are available without prescription. Codeine dependence and subsequent abuse has been reported to occur in people who had initially used over-the-counter products for painful conditions.<sup>17</sup>

### **Conclusion**

Codeine's use as an analgesic is confounded by variable pharmacokinetics that make its efficacy and safety difficult to predict in an individual.

The limited efficacy seen in clinical trials, even at higher doses, is disappointing and raises questions as to the value of the low-dose combination preparations available in Australia. In many instances where a combination containing codeine has been prescribed, treatment with paracetamol or an NSAID may have been just as effective. In cases where there is a genuine need for stronger analgesia, treatment with a low dose of the active metabolite morphine (or one of the synthetic alternatives) provides a more predictable response.

While codeine's adverse effects are generally troublesome rather than serious, there are reports of serious adverse events and fatalities. The potential for drug dependence and misuse, resulting in toxicity from the paracetamol or NSAIDs used in combination products, also raises concerns regarding the availability of codeine in the community. As with any medicine,

due care should be taken in recommending or prescribing this drug. In other words, take caution with codeine.

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*Conflict of interest: none declared*

## Self-test questions

*The following statements are either true or false (answers on page xx)*

3. Patients who are ultrafast metabolisers of codeine need higher doses to obtain satisfactory analgesia.
4. The dose of codeine found in over-the-counter products is too low to cause drug dependence.

## Dental notes

### Cautions with codeine

Patients who present with profound dental pain often do not require prescribed analgesics if they are treated promptly by a dentist. In the vast majority of presentations, the dental treatment will manage the patients' pain. Nevertheless, although the prescription of an analgesic for ongoing pain management is often not required, professional advice about the most appropriate and effective over-the-counter medicine to use is a professional courtesy we should offer to our patients.

The considerable inter-individual variation in the effectiveness of codeine, combined with its rare, but potentially serious, adverse events, suggests that codeine for dental pain should be avoided. Patients with ongoing pain and who are able to use a non-steroidal anti-inflammatory drug, such as ibuprofen, are

likely to have more predictable control of their pain. The pain management strategies outlined in Therapeutic Guidelines, Oral and Dental<sup>1</sup> provide clear advice to help patients manage their pain or their expected pain, following dental treatment.

The warning 'take caution with codeine' should resound in the dental setting, particularly with patients who specifically request opioid drugs as an alternative to adequate dental treatment.

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