How codeine metabolism affects its clinical use

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A deeper understanding of codeine's unique pharmacokinetic profile is required to ensure the best analgesic outcomes for patients.

Opioid analgesics

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Despite its utility and ubiquity, codeine actually has little or no analgesic activity until it is metabolised into morphine
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After reading this article, you should be able to:

- Appreciate that codeine is a prodrug, which is metabolised into morphine;
- Understand that codeine's conversion into morphine shows significant variability and is influenced by many factors;
- Comprehend the clinical consequences of such variable metabolism;
- Monitor patients taking codeine, and consider when alternative opioids may be appropriate.

Codeine is an established, familiar and widely used analgesic. It is considered a weak opioid, with a potency around one tenth that of morphine (i.e. 60mg of codeine is equivalent to around 6mg of morphine)[1]. Codeine is administered in doses of 15–60mg up to four times per day (maximum of 240mg in 24 hours) and confers beneficial analgesic, antitussive and antidiarrhoeal effects[2,3].

Despite its utility and ubiquity, codeine actually has little or no analgesic activity until it is metabolised into morphine[4,5]. Consequently, codeine can be regarded as a prodrug (a compound that is pharmacologically inactive until it is metabolised into an active form by the human body)[6].

The extent of this metabolism varies however: individuals with differing CYP2D6 enzyme activity may derive differing effects (and associated adverse effects) from the same dose of codeine. Additional limitations include the potential for drug–drug interactions, and a so-called ‘ceiling effect’ that adversely tips the risk–benefit scale at supratherapeutic doses[2,3,6]. To appreciate the wide-ranging clinical significance of these factors fully, the metabolism of codeine must first be understood.

Metabolism

Codeine is primarily metabolised by two different pathways (see Figure)[2]. In most people, around 80% of codeine is conjugated to form codeine-6-glucuronide, which may have weak analgesic activity[2,7]. However, typicallyless than 10% of codeine undergoes CYP2D6-mediated O-demethylation to the potent analgesic, morphine[5].

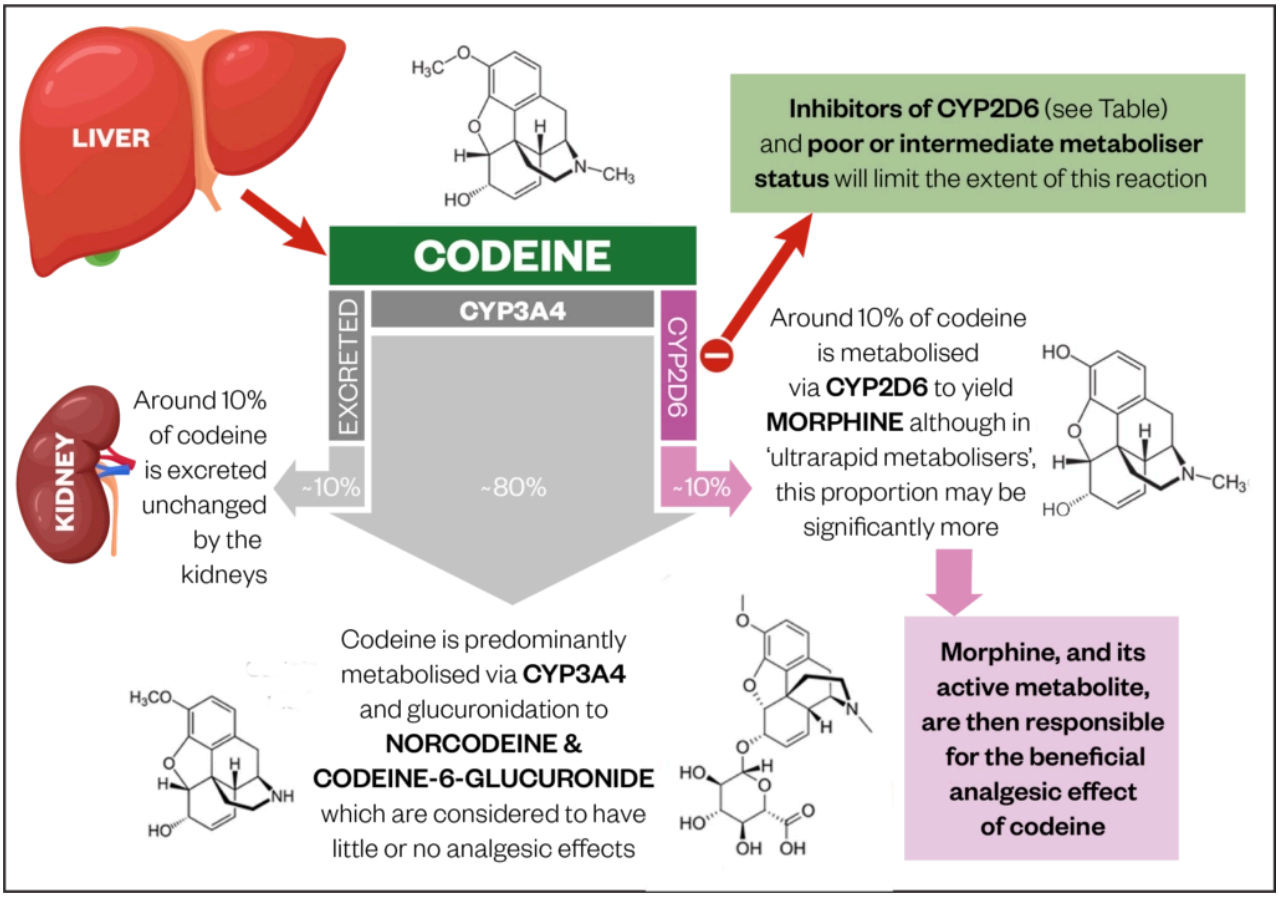

Figure. The hepatic metabolism of codeine
Source: J Pickard and J Hindmarsh, adapted from Gasche *et al*.[8]

The CYP2D6 enzyme belongs to the CYP450 super-family of enzymes, which are responsible for the metabolism of many drugs and endogenous compounds[9].

These enzymes exist throughout the body, but are most prevalent in the liver. The expression and function of these enzymes can be altered by genetic variation, with large inter-ethnic differences being observed[10]. For example, clinically significant alterations in CYP2D6 functionality are known to affect Caucasians (5–10%) and Africans (0–34%) more than Asians (≤1%)[10–12].

Such variations can significantly affect how an individual responds to a drug[11]. This can be said to be true of codeine[9,10]. The extent of that conversion can vary from none to potentially too much, meaning that, for some people, codeine may not be the right choice of analgesic[8,13–15].

Identifying CYP2D6 metabolism status

Although pharmacogenetic testing can determine a patient's genotype and CYP2D6 functionality, in practice, such testing has not been shown to be cost effective and is therefore not routinely employed prior to initiating drugs such as codeine[10–12]. Nevertheless, as differing CYP2D6 metaboliser statuses can have clinically observable consequences for patients, it remains important to understand how the metabolism of codeine can be affected by these genetic differences. CYP2D6 statuses are classified as poor, intermediate, extensive or ultra-rapid(see Box)[10,13].

Box: CYP2D6 statuses and the associated analgesic benefit versus potential adverse effects

- **Poor metabolisers** (5–10% of individuals) lack functional enzymes and will thus derive little to no analgesic benefit from codeine, owing to an inability to convert it into its active form, morphine[10,13]. Poor metabolisers still experience similar rates of adverse effects (such as sedation, dizziness, euphoria, blurred vision and dry mouth) from codeine when compared with the general population[14,15]. This subset of individuals may experience undesirable effects, without any clinical analgesic benefit.
- **Intermediate metabolisers** (2–11% of individuals) may express enzymes with decreased function or have a combination of functioning and non-functioning enzymes[10,13]. Consequently, drug metabolism may be reduced, and such individuals may also derive little benefit from codeine[10,13].
- Most individuals (77–92%) are **extensive metabolisers**.They have normal enzyme activity, and will metabolise around 10% of codeine to morphine, deriving analgesic benefit[13].
- A rarer, but not-to-be-overlooked subset (1–2% of individuals) are considered **ultra-rapid metabolisers**. Ultra-rapid metabolisers have increased enzymatic activity, which leads to them metabolising a greater proportion of codeine into morphine than the general population[10,13]. This is potentially very hazardous: Gasche *et al*. described a case of life-threatening opioid toxicity in a man aged 62 years who had received a low dose of codeine (75mg per day) for management of cough[8]. The patient was later identified as being a CYP2D6 ultra-rapid metaboliser. Unfortunately, similar cases have been reported in children, some of which have resulted in fatalities[16]. Consequently, codeine for management of pain, cough and diarrhoea is contraindicated in patients aged under 12 years[17,18].

Hence, up to nearly a quarter of individuals may show a response to codeine that ranges from inefficacy — but still with adverse effects — to potentially life-threatening toxicity[11].

In practice, the CYP2D6 metabolism status of patients can be determined through clinical observation. Poor metabolisers may experience limited to no therapeutic response to codeine (also see drug–drug interactions below), while those displaying signs of opioid toxicity — such as respiratory depression, myoclonic twitches, confusion and hallucinations — may be ultra-rapid metabolisers[8,13,17]. In both cases, the most appropriate course of action may be to discontinue codeine and decide, along with the patient and prescriber, on an alternative analgesic. For example, pharmacists can liaise with prescribers and suggest starting low-dose morphine (10mg modified-release morphine sulphate twice daily) in place of codeine, if appropriate. If the patient is thought to be a poor metaboliser, a ‘wash out’ period does not need to be observed, but if toxicity to codeine is suspected, prescribers should wait for signs of toxicity to abate as the drug washes out before prescribing an alternative. In the latter scenario, specialist input is advised[1,13,19].

Metabolism status aside, the co-administration of drugs that alter the function of CYP2D6 must also be considered as an important determinant of the variable efficacy of codeine.

Drug–drug interactions

Medications that inhibit CYP2D6 are predicted to diminish, or abolish, the effect of codeine by preventing its metabolism into morphine. These are outlined in the Table [15,20]. Therefore, regardless of CYP2D6 status, inefficacy of codeine may occur as a result of a drug–drug interaction. Patients reporting limited to no therapeutic reponse from codeine should also have their medications reviewed for the presence of CYP2D6 inhibitors (see Table). For people taking CYP2D6 inhibitors, conversion to an alternate opioid which does not rely on CYP2D6 metabolism (e.g. morphine) should be considered [20,21].

Common CYP2D6 inhibitors	
CYP2D6 inhibitors	**Suggested action**
Abiraterone Bupropion Cinacalcet Fluoxetine Paroxetine Quinidine Ritonavir Terbinafine	Monitor for analgesic efficacy and consider using an alternative analgesic to codeine in the case of reduced efficacy
Source: Stockley's drug interactions[20]	

Table: Common CYP2D6 inhibitors

The 'ceiling' effect

When used for the management of pain, codeine is generally considered to have a 'ceiling' effect. Although this is not an absolute ceiling, this term describes a point where the analgesic benefit of further dose escalation is often outweighed by the increasing burden of adverse effects, thus limiting dose escalation beyond a certain point[21–26]. Doses of codeine should not exceed the licensed maximum of 240mg in 24 hours (in divided doses)[3]. This maximum has been derived in part from studies indicating that dose escalations beyond this point cause an increase in adverse effects —including sedation, dizziness, nausea and vomiting — with limited additional analgesic efficacy[21–26]. In practice, the ceiling effect is circumvented by prescribing within the licensed therapeutic window.

As doses can vary between 15–60mg up to 4 times per day, it is important that patients are counselled on the strength and number of tablets they need to take and that a minimum of 6 hours should pass before taking the next dose[2,3].

Monitoring

When reviewing patients, the analgesic benefit of codeine should be determined by asking patients to score their pain out of ten (where ten represents the worst pain imaginable) and assess for improvement post initiation of codeine. Additionally, functional and behavioural outcomes which may also infer analgesic response should be evaluated (e.g. if the patient reports increased physical activity, owing to a reduction in pain).

Patients should be closely monitored for adverse effects, therapeutic response and the balance between the two. Many adverse effects can be dose limiting (e.g. confusion, dizziness, hallucinations, nausea and vomiting)[1]. Constipation and dry mouth are class effects of all opioids, to which tolerance does not develop and should be managed accordingly depending on severity[1].

Patients should be informed that codeine can cause drowsiness, which may affect the performance of skilled tasks, such as driving[1]. Such sedative effects can also be enhanced by alcohol and other sedative medications (e.g. benzodiazepines)[20,21]. Patients should not drive at the start of codeine therapy, or following a dose titration [27,28]. In both cases, it may take five days, or more, for the drowsiness to resolve and patients should only drive if they feel 100% safe to do so[29].

Concomitant use of codeine and other opioids (such as tramadol, morphine, oxycodone, hydromorphone or fentanyl) or opioid-containing preparations (such as over-the-counter co-codamol) can increase the risk of opioid toxicity. Pharmacists should ensure patients are made aware that codeine is an opioid and that use alongside other opioids should be avoided[1,20].

It is important that patients and carers are counselled on how to recognise the signs and symptoms of opioid toxicity (including reduced consciousness, somnolence, respiratory depression, ‘pin-point’ pupils, nausea and vomiting). In such an event, urgent medical attention should be sought. The risk of respiratory depression is also increased when opioids are used alongside benzodiazepines and/or gabapentinoids[3,15,30,31].

Alternative solutions

Codeine’s latent and unpredictable spectrum of efficacy, susceptibility for interaction with common medications and a ‘ceiling’ limiting dose escalations must be kept in mind by prescribers. Use of alternative opioids with superior efficacy and safety should be considered; particularly for cancer pain and in paediatrics and post-operative settings [27,28,30–32].

Getting around these issues can be simple, however: for cancer pain, evidence now advocates ‘skipping the prodrug’ and substituting codeine with low-dose morphine, which was shown to be superior to codeine, with patients achieving greater and more rapid onset of pain reduction with morphine than with codeine[32]. Some studies in neurosurgery have also shown greater patient satisfaction with morphine compared with

codeine[33]. In paediatrics and palliative care, it has become commonplace to avoid ‘weak’ opioids in favour of initiating low doses of ‘strong’ opioids, such as morphine[29,34] .Oral morphine is also commonly used post-operatively in preference to codeine[35].

Overall, codeine remains established, accessible and — in the majority — effective as an analgesic, but it is important to remain mindful of its limitations. Garnering the most beneficial effects through its metabolism to morphine, prescribers should consider carefully when alternatives to codeine as a weak opioid may be favourable, more predictable or safer.

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