



Combination analgesics in adults

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Summary

Many analgesic products contain combinations of different drugs. There are few direct comparisons of these combinations, but several appear to be no more effective than an appropriate dose of one of their individual analgesic components. Many combinations should be avoided because they contain drugs that have significant adverse effects or that do not contribute to the analgesic effect. Some combinations can be obtained without a prescription. Patients may inadvertently overdose themselves if they take several of these products simultaneously.

Key words: aspirin, codeine, dextropropoxyphene, NSAIDs, paracetamol.

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Introduction

There are at least 40 different combination analgesic preparations available in Australia. Most of these are combinations of paracetamol 500 mg with codeine in doses ranging from 8 mg to 30 mg.¹ A number of preparations also contain doxylamine, a sedating antihistamine with anticholinergic effects.² There are also other preparations available which contain paracetamol and dextropropoxyphene, aspirin and codeine, aspirin and dihydrocodeine, and ibuprofen and codeine.¹ Internationally, preparations containing paracetamol with other opioids such as oxycodone and tramadol are available.

Regulation

The Australian scheduling of combination analgesics under poisons regulations is determined by the dose of codeine per tablet, the number of tablets in a pack, and the other drugs in the combination (for example doxylamine). All preparations containing 30 mg codeine in combination with paracetamol or aspirin are Schedule 4. They therefore require a prescription. Preparations with doses of codeine 15 mg or less have been available as Schedule 2 (pharmacy medicine) or 3 (pharmacist-only medicine), but from 1 May 2010 they were no longer available in Schedule 2. Combination analgesics containing up to 12 mg codeine are pharmacist-only, and those containing more than 12 mg are prescription-only. The pharmacist-only products are limited to no more than five days of treatment.³

Evidence of efficacy

Paracetamol or a non-steroidal anti-inflammatory drug (NSAID) given with a strong opioid such as morphine in a multimodal analgesic regimen for acute pain, reduces the amount of opioid used, improves analgesia and reduces the duration of patient-controlled analgesia.⁴ However, data supporting products which combine a weak opioid, such as codeine, with paracetamol or an NSAID, are limited. There is much variability in the dose of weak opioid contained in combination products, and the role of codeine in managing acute pain is unclear. Analgesic guidelines state that 'although codeine is widely used, its place in therapy is uncertain'.⁵ The National Prescribing Service (NPS) has stated that 'studies in acute pain suggest only modest additional analgesic efficacy when a weak opioid is added to paracetamol, but a higher rate of adverse effects after repeated doses'.⁶ There is consensus that paracetamol is the first-line treatment for many acute pain states.^{4–8}

The Oxford Pain group has developed a league table of analgesic efficacy for most common oral analgesics. This uses data from systematic reviews of randomised, double-blind, single-dose studies of patients with moderate to severe pain where the outcome is a reduction of pain by at least 50% in 4–6 hours. Data are expressed as:

- the number of patients who need to be treated (NNT) for one to get 50% relief
- the percentage of patients with at least 50% pain relief (Table 1).

There are limitations to these data. Often the trial sample size is small so there may be wide confidence intervals, they are not head-to-head comparisons, adverse events are not reported and the trials are single-dose studies. The table does not contain information about all the analgesic combinations available in Australia, and includes information about products which are not available here. However, the table provides the best available comparative information.⁹

Paracetamol with codeine

A Cochrane review found that paracetamol with codeine is more effective in acute postoperative pain than paracetamol alone. The NNT to achieve 50% pain relief at 4–6 hours was 2.2 for paracetamol 1 g with codeine 60 mg. Paracetamol 1 g alone has an NNT of 3.8, but paracetamol 600 mg in combination with codeine 60 mg has an NNT of 4.2.^{9,10} Although the dose of codeine required to provide any analgesic effect is unclear, it

Table 1

Efficacy of oral analgesics *

Analgesic (mg)	Number of patients in comparison	Percent with at least 50% pain relief	NNT †	Confidence intervals
Paracetamol 1000 + codeine 60	197	57	2.2	1.7–2.9
Paracetamol 600/650 + codeine 60	1123	42	4.2	3.4–5.3
Paracetamol 300 + codeine 30	379	26	5.7	4.0–9.8
Paracetamol 500 + oxycodone IR 10	315	66	2.6	2.0–3.5
Paracetamol 500 + oxycodone IR 5	150	60	2.2	1.7–3.2
Paracetamol 325 + oxycodone IR 5	149	24	5.5	3.4–14.0
Paracetamol 650 + tramadol 75	679	43	2.6	2.3–3.0
Paracetamol 650 + dextropropoxyphene (65 mg hydrochloride or 100 mg napsylate)	963	38	4.4	3.5–5.6
Aspirin 650 + codeine 60	598	25	5.3	4.1–7.4
Aspirin 600/650	5061	38	4.4	4.0–4.9
Codeine 60	1305	15	16.7	11–48
Paracetamol 1000	2759	46	3.8	3.4–4.4
Tramadol 100	882	30	4.8	3.8–6.1
Ibuprofen 200	3248	48	2.7	2.5–2.9

* Modified from the Oxford league table⁹

† Numbers needed to treat (NNT) are calculated for the proportion of patients with at least 50% pain relief over 4–6 hours compared with placebo in randomised, double-blind, single-dose studies in patients with moderate to severe pain

IR Immediate-release formulation

is believed that a minimum dose of 30 mg codeine is required. The majority of combination products available in Australia contain doses of codeine less than this.⁵

In contrast, the National Health and Medical Research Council review of evidence for the management of acute musculoskeletal pain said that there is insufficient evidence to recommend the use of opioids or compound analgesics (paracetamol/codeine combinations) in acute low back pain, acute neck pain, acute shoulder pain or acute knee pain. It reports that, in general, opioids and compound analgesics have a substantially increased risk of adverse effects compared with paracetamol alone.⁷

For dental pain, the most effective approach is to undertake appropriate dental treatment. After dental extraction the efficacy of NSAIDs is superior to that of combinations of paracetamol and codeine.^{11,12} The Therapeutic Guidelines: Oral and Dental recommend that if a combination is used, the dose of codeine should be at least 25 mg and suggest that a codeine dose of 60 mg with paracetamol 1 g will be required for severe dental pain.¹¹

Dextropropoxyphene

Overdoses of dextropropoxyphene can be fatal. There are concerns about accumulation of a toxic metabolite of dextropropoxyphene in patients with renal impairment.⁵ The

drug has been withdrawn in the UK and is being withdrawn in New Zealand.

Dextropropoxyphene is a weak opioid, but in combination with paracetamol it provides no increase in analgesia and has more adverse effects than paracetamol alone.⁵ The Oxford league table shows that dextropropoxyphene 65 mg in combination with paracetamol 650 mg has an NNT of 4.4.⁹

Doxylamine

There is no evidence that doxylamine has any analgesic efficacy, but this sedating antihistamine may be a component of compound analgesics. Doxylamine may be subject to abuse and combination analgesic preparations containing it cannot be recommended.

Opioids in combination with NSAIDs

While there is a significant body of evidence identifying the efficacy of NSAIDs in acute pain, there are limited data on combining them with opioids. Many NSAIDs, in single-dose studies, show greater efficacy than codeine in combination with paracetamol or codeine in combination with aspirin.⁹ Aspirin 650 mg in combination with codeine 60 mg is effective in postoperative pain with an NNT of 5.3 for at least 50% pain relief over 4–6 hours in patients with moderate to severe pain compared with placebo. This appears to be less effective than

a 650 mg dose of aspirin alone (NNT 4.4) but the statistical confidence intervals overlap.⁹ Codeine 60 mg may enhance the analgesic effect of ibuprofen 400 mg, however data are lacking to compare the Australian formulation of codeine 12.8 mg with ibuprofen 200 mg to ibuprofen 200 mg alone.¹³

Chronic pain

The evidence for long-term efficacy of opioids in chronic pain is limited. Opioids should only be considered as a component of a multidimensional management plan. In general, opioids other than codeine should be chosen. One exception is osteoarthritis of the hip, for which there is some evidence for efficacy of codeine.⁵

Opioid analgesics should be avoided in headache because of the risk of dependence and medication overuse headache.^{4,8}

Adverse effects and toxicity

Opioids and compound analgesics have a substantially increased risk of adverse effects compared with paracetamol alone.⁷ These adverse effects include constipation, nausea, vomiting and drowsiness. The elderly appear to be more susceptible to adverse effects.⁵ Abuse of, and dependence on, codeine-containing combination analgesics is a poorly quantified, but likely significant, risk.¹⁴ Codeine is converted to morphine by cytochrome P450 2D6, but 7–10% of the Caucasian population lack this enzyme. These 'poor metabolisers' of codeine will get no analgesic benefit, but may experience adverse effects.⁵

A significant proportion of cases of acute liver failure are from unintentional paracetamol overdose. Many of these patients have taken more than one paracetamol-containing preparation simultaneously.¹⁵

Conclusion

In summary, for acute postoperative pain there is evidence of efficacy for paracetamol 1 g with codeine 60 mg, and some evidence for paracetamol combined with codeine in hip osteoarthroses. Current guidelines do not support the use of paracetamol and codeine combination products in other acute or chronic pain states. There are limited data for doses of codeine less than 60 mg in combination with paracetamol, and current data suggest that paracetamol alone has greater efficacy than paracetamol combined with codeine at doses under 60 mg. Current evidence shows improved analgesia with codeine 60 mg and ibuprofen 400 mg compared to ibuprofen alone, but there are minimal data for lower doses. Indirect comparisons show that the combination of aspirin and codeine may be less efficacious than aspirin alone and therefore the combination cannot be recommended. Given the lack of documented analgesic efficacy of low-dose codeine preparations, rescheduling of codeine in Australia is unlikely to impact significantly on analgesic options, but may reduce the harms from overuse.

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Further reading

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See **Dental note** p.107, and information for consumers on this article at www.australianprescriber.com

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