Analgesic efficacy and safety of paracetamol-codeine combinations versus paracetamol alone: a systematic review


Authors' objectives
To assess the safety and analgesic effects of paracetamol plus codeine combinations versus paracetamol alone.

Searching
MEDLINE was searched from 1964 to 1995, International Pharmaceutical Abstracts from 1965 to 1991, BIOSIS Previews from 1970 to 1991, and EMBASE from 1983 to 1995. References lists of articles were also examined, and manufacturers of combined paracetamol and codeine formulations were contacted.

Study selection
Study designs of evaluations included in the review
Controlled clinical trials and randomised controlled trials were included.

Specific interventions included in the review
Paracetamol in doses ranging from 400 to 1000 mg, and codeine in mainly 60 mg doses. One trial used suppositories, while the others used oral medication (tablets or capsules).

Participants included in the review
All but two trials examined pain in surgical patients; one trial examined pain in children.

Outcomes assessed in the review
Pain intensity and pain relief, as measured by visual analogue or other quantitative rating scales in the primary studies. Four measures of pain relief were used: sum pain intensity difference (sum of differences between treatment and control groups, as noted at all different time points in the post-drug observation period), peak pain intensity difference (maximum pain intensity difference at any time during the observation period), total pain relief (summed pain relief over all time points), and peak pain relief (maximum pain relief experienced at any time point during the observation period).

Side-effects were assessed in terms of patients reporting at least 1 event, and the number of patients with an adverse reaction. The numbers of individual events were also reported: dizziness, drowsiness, nausea, vomiting, constipation and 'other'.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The quality of all trials was scored using a checklist of methodological criteria. These scores were used as weights in the analyses of efficacy. At least two reviewers assessed the papers independently.

Data extraction
Efficacy measures were converted to a percentage scale in order to standardise for the different scales used in the trials. Measures of summed pain relief, i.e. the sum of the differences in pain relief noted at each time point in the study, were adjusted for the number of time points within the observation period.
Methods of synthesis
How were the studies combined?
Weighted mean effects were calculated using the sample sizes as weights. These analyses were repeated using the quality scores as weights.

How were differences between studies investigated?
One sample t-tests were performed to test for differences in efficacy between treatments. Standard meta-analytical tests for homogeneity were not possible due to the lack of standard deviations and standard errors reported in the primary studies. For the safety analyses, a DerSimonian and Laird random-effects model (see Other Publications of Related Interest) was used to assess differences in incidence of side-effects.

Results of the review
Twenty-four published trials were included. The total number of patients involved was not given.

Only single-dose studies could be combined to assess efficacy. These showed that codeine added to paracetamol provided a 5% increase in analgesia on the sum pain intensity difference. This was comparable to the difference in analgesic effect between codeine and placebo. The combination remained more effective than paracetamol alone at different dosages of the 2 drugs. In terms of side-effects, there was no difference between paracetamol alone and combination therapy in single-dose studies. The multi-dose studies showed an increase in reported side-effects with combination therapy.

Authors' conclusions
Paracetamol plus codeine preparations produce a significant increase in analgesia compared with paracetamol alone. Thus, for occasional pain relief this combination therapy may be appropriate, though repeated use increases the occurrence of side-effects.

CRD commentary
There is a lack of information on the characteristics or quality of individual studies reported in the paper. This makes it difficult to determine the generalisability of the findings. However, the review appears to provide a methodically-sound assessment of the effectiveness of these combined analgesics.

Additional tables relating to this review are available on the BMJ website. See Web Address at end of abstract.

Implications of the review for practice and research
Future studies should record the proportion of patients experiencing good or moderate pain relief, as this information appears not to be reported in current studies. No studies were found which evaluated the efficacy of the most common UK dose of codeine (8 mg) used in combination with paracetamol. Studies of this particular codeine dosage would be useful to determine whether it is less effective, but with fewer side-effects.

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Other publications of related interest

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