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

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Abstract

Objectives—To assess whether adding codeine to paracetamol has an additive analgesic effect; to assess the safety of paracetamol-codeine combinations versus paracetamol alone.

Design—Systematic literature review with meta-analysis, methodological quality of published trials being scored by means of 13 predefined criteria.

Trials—24 of 29 trials that met the inclusion criteria. Models studied in the trials were postsurgical pain (21), postpartum pain (one), osteoarthritis pain (one), and experimentally induced pain (one).

Interventions—Dosages ranged from 400 to 1000 mg paracetamol and 10 to 60 mg codeine.

Main outcome measures—The sum pain intensity difference (efficacy analysis) and the proportion of patients reporting a side effect (safety analysis).

Results—Most trials were considered of good to very good quality. Only the single dose studies could be combined for analysis of analgesic efficacy. Pooled efficacy results indicated that codeine added to paracetamol provided a 5% increase in analgesia on the sum pain intensity difference. This effect was comparable to the difference in analgesic effect between codeine and placebo. The cumulative incidence of side effects with each treatment was comparable in the single dose trials. In the multidose studies a significantly higher proportion of side effects occurred with paracetamol-codeine preparations.

Conclusion—The difference in analgesic effect between paracetamol-codeine combinations and paracetamol alone was small but statistically significant. In the multidose studies the proportion of patients reporting a side effect was significantly higher with paracetamol-codeine combinations. For occasional pain relief a paracetamol-codeine combination might be appropriate but repeated use increases the occurrence of side effects.

Introduction

Paracetamol is well tolerated and available without prescription. Over the years it has gained a prominent place as an over the counter analgesic, especially after aspirin was found to be associated with Reye's syndrome in young children.¹ Paracetamol is also commonly used in hospital. When pain relief is insufficient with paracetamol alone codeine may be added in combination. Codeine acts at several sites within the central nervous system.² The mechanism of action of paracetamol is less well understood than that of codeine. Most of the analgesic effect of paracetamol is thought to be mediated peripherally,^{3,4} though recent evidence also suggests a direct action within the central nervous system.^{5,6}

The rationale for combining two analgesics with presumably different mechanisms of action is the theoretical enhancement of efficacy.⁷ Combining two differently acting analgesics avoids increasing the dose of either drug used alone and therefore has a lower expected incidence of side effects.^{3,8} A literature search disclosed no systematic review on this topic. We conducted a systematic review of published trials to determine the value of codeine added to paracetamol in the relief of pain with regard to both efficacy and safety.

Methods

LITERATURE SEARCH AND INCLUSION CRITERIA

Published trials were located by various strategies. Computer searches of Medline (1964-95), International Pharmaceutical Abstracts (1965-91), and Biosis (1970-91) with keywords acetaminophen, paracetamol, codeine, and pain were combined with an Embase (1983-95) search with keywords acetaminophen, paracetamol, codeine, and analgesic agents. Other publications were found by reviewing reference lists and by correspondence with manufacturers of paracetamol-codeine preparations. Criteria for inclusion were (a) equal dosage of paracetamol in the paracetamol-codeine and paracetamol only groups, (b) controlled clinical trial or randomised controlled trial, and (c) only codeine added to paracetamol (not caffeine).

QUALITY ASSESSMENT

Methodological quality of all trials was scored by using a list of 13 predefined methodological criteria. The list was adapted from ter Riet *et al.*⁹ At least two of us independently assessed all studies. Differences in assessment were resolved by discussion. The maximum score was 100 points (see appendix). Weights given to the criteria were based on our assessment of the relative importance of each criterion.

Tables listing the main characteristics of the trials and scores for methodological quality are available from AJMdeC and on the *BMJ's* worldwide web page (<http://www.bmj.com/bmj/>).

DATA EXTRACTION

All relevant data for the evaluation were extracted from text, tables, and figures. Pain intensity and relief of pain were measured by visual analogue or other quantitative rating scales. In most studies the effect of the analgesic on pain intensity at each time point was expressed as the pain intensity difference (PID)—that is, the difference in pain intensity between that time point and baseline. The sum pain intensity difference (SPID) is the sum of the differences noted at all different time points in the postdrug observation period. The peak pain intensity difference (PPID) is the maximum pain intensity difference at any time during the postdrug observation period. Total pain relief (TOTPAR) is the summed pain relief over all time points, and

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peak pain relief (PPAR) is the maximum pain relief experienced at any time point during the postdrug observation period.

STATISTICAL ANALYSIS

Efficacy outcome measurements were converted to a percentage scale to standardise for the different scales used in the trials.¹⁰ Peak pain intensity difference and peak pain relief were converted by the following formula:

$$(\text{presented value [PPID or PPAR]} / (\text{maximal value} - \text{minimal value [on scale]}) \times 100 = \text{value on percentage scale.}$$

For the sum pain intensity difference and total pain relief a similar strategy was followed, extended by adjusting for the number of time points within the observation period. Thus conversion of these outcome measurements to the percentage scale was performed as:

$$(\text{presented value [SPID or TOTPAR]} / (\text{maximal value} - \text{minimal value [on scale]} \times n) \times 100 = \text{value on percentage scale,}$$

where n is the number of measurements within the observation period. The amount of statistical information was limited in many reports. Typically only means were given with no standard deviation or standard error.

The n weighted mean effect, used in all our efficacy analyses, is the mean effect of all studies with the sample size of the study taken as relative weight. Because the standard deviation or standard error of individual results was often not reported standard meta-analytical techniques, including testing for homogeneity, could not be employed. To test whether differences between treatments were significant one sample t tests were performed. The variance of the n weighted mean was estimated as:

$$\text{Variance } (\bar{y}) = \frac{\sum_{i=1}^k n_i \times (y_i - \bar{y})^2}{(k-1) \times \sum_{i=1}^k n_i}$$

where $\bar{y}$ is the n weighted mean effect, n_i is the number of patients in the i^{th} study, y_i is the effect in the i^{th} study, and k is the number of studies. A 95% confidence interval was constructed around the mean difference by using the t distribution with $(k-1)$ degrees of freedom. Efficacy analyses were repeated by using the quality score as an additional weighting factor. For safety analyses the DerSimonian and Laird random effects model¹¹ was used to assess differences in the occurrence of side effects.

Results

Twenty nine published trials satisfied the inclusion criteria. Five reports were excluded from analysis: two abstracts were later published as full papers,^{12,13} one report was a summary of an earlier published trial,¹⁴ and in two reports the abstract and text differed in the dose of paracetamol used.^{15,16} The 24 studies included in the review were assessed for methodological quality.¹⁷⁻⁴⁰ Differences in the assessments were resolved by discussion and the assessors reached full agreement in all cases. The quality of the trials ranged from average to very good, 12 trials scoring 75 or more on the 100 point scale.

Twenty one trials employed a single dose design. All but two of the single dose trials used postsurgical pain as the model to evaluate the drugs. The dosages used for paracetamol varied from 400 to 1000 mg. Most studies used a codeine dose of 60 mg. Fourteen trials compared a paracetamol-codeine combination with paracetamol alone as a main objective. The duration of observation in the single dose trials ranged from two to 12 hours. Only one trial used suppositories, the other trials using oral agents (tablets in nine, capsules in seven; in seven trials the oral agent was not specified). In most studies the treatment was taken when pain was moderate or severe. As almost all studies used postsurgical pain as the model we assumed the natural time course of the pain to be comparable among studies.

Table 1—Analgesic efficacy of paracetamol-codeine combinations, paracetamol, codeine, and placebo

Scale	No of studies	Treatment 1†		Treatment 2†		n Weighted % difference	95% Confidence interval
		No of patients	%	No of patients	%		
Sum pain intensity difference							
ParCod - Par	19	678	22	678	16	5.5	4.9 to 6.2
ParCod - Cod	6	212	25	164	12	12.3	10.9 to 13.8
ParCod - Plac	16	522	23	492	5	17.8	16.7 to 19.0
Par - Cod	6	210	17	164	12	4.8	2.1 to 7.4
Par - Plac	16	526	17	492	4	12.4	11.5 to 13.4
Cod - Plac	5	141	14	131	6	8.5	1.9 to 15.1
Peak pain intensity difference							
ParCod - Par	12	426	38	430	31	7.1	5.5 to 9.0
ParCod - Cod	3	126	33	84	19	14.1	-12.5 to 40.7
ParCod - Plac	10	344	40	329	14	25.6	19.4 to 31.9
Par - Cod	3	126	28	84	19	8.6	-7.9 to 25.1
Par - Plac	10	353	31	329	14	16.7	12.4 to 21.0
Cod - Plac	2	61	17	56	12	4.7	-83.5 to 93.8
Total pain relief							
ParCod - Par	15	511	43	515	38	5.6	4.5 to 6.8
ParCod - Cod	4	156	45	112	29	16.3	13.1 to 19.5
ParCod - Plac	14	466	43	447	26	17.1	14.7 to 19.5
Par - Cod	4	154	40	112	29	10.7	5.0 to 16.4
Par - Plac	14	470	37	447	26	11.2	9.8 to 13.4
Cod - Plac	3	84	29	86	23	5.6	2.0 to 13.1
Peak pain relief							
ParCod - Par	12	426	59	430	52	7.3	5.6 to 9.0
ParCod - Cod	3	126	63	84	47	16.3	2.9 to 29.7
ParCod - Plac	10	344	62	329	31	31.0	28.4 to 33.6
Par - Cod	3	126	57	84	46	10.8	-1.3 to 23.0
Par - Plac	10	353	53	329	31	21.2	19.2 to 23.2
Cod - Plac	2	61	42	56	32	9.6	-17.7 to 37.0

ParCod = Paracetamol-codeine combination. Par = Paracetamol. Cod = Codeine. Plac = Placebo.

†Treatment 1 denotes agents on left in scale column; treatment 2 denotes agents on right in scale column.

EFFICACY

Three single dose studies^{33 39 40} and two multidose studies^{18 35} were excluded from the pooled efficacy analysis because the data provided could not be combined. Of the single dose studies, one evaluated both treatments in 12 volunteers with laser induced pain and found paracetamol plus codeine to be slightly more effective.³³ A study in children after tonsillectomy³⁹ found the combination no more effective than paracetamol alone. Beaver and Feise assessed the analgesic effect of 600 mg paracetamol, 60 mg codeine, and a combination of the two in patients with postoperative pain. The analgesic effect of the combination was almost equal to the sum of analgesia produced with the two agents given separately.⁴⁰ In a four week multidose trial Kjaersgaard-Andersen *et al* found a significant difference between the paracetamol-codeine group and the paracetamol alone group only in the first week.¹⁸ The last experiment with results that could not be combined compared different doses of codeine added to a standard dose of paracetamol.³⁵ A superior analgesic effect was found with the paracetamol-codeine combination.

Of the 19 trials in the pooled analysis, one employed a multidose design³² and the others a single dose design. Data on efficacy in the multidose trial could be combined only for the first treatment, so resulting in a single dose study.

Results of the pooled analysis showed that the paracetamol-codeine combination scored significantly higher than paracetamol alone on all four measures of efficacy (table 1). Some studies included an additional placebo or codeine control group. Comparing all possible combinations showed that the increase in efficacy with the paracetamol-codeine combination versus paracetamol alone was no different from the increase with codeine versus placebo. On all measures of efficacy paracetamol-codeine versus placebo showed the greatest difference. Including the quality score of the trial as an additional weighting factor in the analysis did not change the results.

In order to assess whether different dosages of paracetamol and codeine yielded different effect estimates, the 19 single dose studies were divided into three categories and the effect estimates assessed in each. Studies of 1000 mg paracetamol with 60 mg codeine^{17 19 28} gave a sum pain intensity difference of 4.2%, studies of 600 or 650 mg paracetamol with 60 mg codeine^{20-27 29 30 34 38} a sum pain intensity difference of 5.3%, and studies with a variable amount of

paracetamol and 30 mg codeine^{31 32 37} a sum pain intensity difference of 7.0%. All these differences favoured the paracetamol-codeine combination.

Restricting analysis to studies in which paracetamol alone and a paracetamol-codeine combination were used as controls for another agent showed a marginal increase in all four measures of efficacy. Restricting analysis to trials using the third molar extraction model showed a small decrease in all measurements of effect. Restricting analysis to studies in which 60 mg codeine was used in the combined preparation, or which had a quality score of at least 75, or which specified using tablets or capsules did not change the sizes of effect.

SAFETY

Of the 24 trials eligible for the safety analysis, six were excluded because they did not provide safety data or safety data were not categorised per treatment group.^{21 25 37-40} Pooled analyses of the occurrence of side effects did not reject the assumption of homogeneity across single dose and multidose studies. Table 2 gives the pooled safety results for single dose and multidose studies. The 15 single dose studies showed no significant difference between paracetamol-codeine combinations and paracetamol alone. The three multidose studies showed an increase in reported side effects with paracetamol-codeine. The frequency of dosing in the three studies was, respectively, two tablets three times a day,³² one tablet five times a day,³⁵ and one tablet three times a day.¹⁸ In two studies side effects were reported on the first day,^{32 35} and in the remaining study they were reported during the first week.¹⁸

Discussion

This systematic review shows that in single dose studies adding codeine to paracetamol produced a 5% increase in analgesic effect as measured by the sum pain intensity difference. All other measures of analgesic effect also showed a significant increase. The cumulative incidence of side effects was comparable in both arms of the single dose studies whereas a higher cumulative incidence of side effects was found in the multidose studies. Most trials were considered of good to very good methodological quality. Assessors were not blinded for authors or results, but all assessments can be checked to see whether any bias occurred.

EFFICACY AND SAFETY

The rationale for combining two analgesics with presumably different mechanisms of action is the theoretical enhancement of efficacy. Therapeutic doses of paracetamol do not influence the pharmacokinetics and metabolism of codeine,⁴¹ and codeine has no effect on the metabolism and clearance of paracetamol.⁴² The data do not reject the hypothesis of an additive analgesic effect of codeine because on most measures of efficacy the difference between paracetamol-codeine and paracetamol alone was comparable with that between codeine and placebo. However, comparisons between placebo and codeine were based on only a few studies.

The analgesic effect of codeine is believed to be mediated via hepatic *O*-demethylation to morphine.⁴³ In 6-10% of white people this biotransformation does not occur. The proportion of "slow" metabolisers of codeine in these studies was unknown. Their presence would have reduced any differences between the treatment groups.

Most studies did not use an intention to treat approach in the efficacy analysis. Hence some studies failed to include patients who needed rescue treatment within two hours^{17 24 27 30 36 38} or patients who took no study medication at all.^{17 23 25-27 29 30 34 36 38} Not using an intention to treat approach is considered inappropriate

Table 2—Frequency of side effects in studies of paracetamol-codeine combinations versus paracetamol alone

Source	Paracetamol-codeine combination	Paracetamol	Pooled rate ratio (95% confidence interval)
Single dose studies (n = 15)			
No of patients reporting ≥ 1 event	484	488	1.1 (0.8 to 1.5)
No with adverse reaction	116	100	
No of events:			
Dizziness	14	11	
Drowsiness	39	35	
Nausea	18	17	
Vomiting	6	7	
Other	43	41	
Multidose studies (n = 3)			
No of patients reporting ≥ 1 event	307	164	2.5 (1.5 to 4.2)
No with adverse reaction	122	37	
No of events:			
Dizziness	42	2	
Drowsiness	12	2	
Nausea	69	9	
Vomiting	19	3	
Constipation	17	7	
Other	90	38	

Key messages

- Paracetamol is one of the most commonly used mild analgesics
- Paracetamol-codeine combinations are thought to bring more pain relief than that achieved with paracetamol alone
- Single dose studies show a slightly increased analgesic effect when codeine is added to paracetamol
- In single dosage the incidence of side effects with paracetamol alone and paracetamol plus codeine is similar; in multidose side effects are significantly increased with paracetamol-codeine preparations
- A paracetamol-codeine preparation is recommended when more pain relief is needed with a single dose of a drug; more side effects may occur with multiple dosage

for efficacy analysis because it can lead to a confounded estimate of treatment effects.⁴⁴ The observed difference between paracetamol-codeine and paracetamol alone must therefore be interpreted with caution.

We could not test for homogeneity of the pooled efficacy outcome in the single dose studies. However, separate analysis of the three categories that employed different dose regimens yielded comparable effect estimates. No clear dose-response relation was seen in the reported dose ranges reviewed. This indicates that the pooled analysis of different dosages might have been justified. It was not possible to determine a pooled efficacy outcome for the multidose studies. Kjaersgaard-Andersen *et al* detected a significant difference between the paracetamol-codeine group and the paracetamol alone group only in the first week of a four week study.¹⁸ They thought that this might have resulted from a possible tolerance to codeine. Single dose studies showed no significant increase in patients reporting side effects but in multidose trials an increased cumulative incidence was found. This agrees with the findings of Stewart, who noted that multidose studies have been reliable predictors of the tendency of a drug to cause side effects.⁴⁵

IMPLICATIONS FOR RESEARCH AND PRACTICE

The 10 studies in which comparison between paracetamol-codeine and paracetamol alone was not the main objective showed a small increase in all sizes of effect. Therefore, publication bias is not considered a main source of confounding. All the studies reviewed had fewer than 100 patients per treatment group. Small studies are more likely not to be balanced on important prognostic variables at baseline. In future studies more attention should be paid to ensuring equal distribution of prognostic variables among treatment groups. This can be accomplished either by prestratification for important prognostic variables or by randomising larger numbers of patients. This will result in a more accurate pooled effect estimate.

We could not assess the proportion of patients with moderate or good pain relief in these studies, as these data were not reported. Pain relief at certain time points in the postdrug observation period was recorded in 15 of the 19 trials included in the pooled efficacy analysis but was usually presented as total pain relief and peak pain relief. In future studies the proportion of patients achieving good or moderate pain relief should be reported.

The commonest combined tablet in the United Kingdom is paracetamol 500 mg with only 8 mg codeine. Most studies in this review added 60 mg codeine to the paracetamol. No controlled trial of 8 mg

codeine added to paracetamol has been reported. It is likely that a reduced dose of codeine has less efficacy and a better safety profile.

Conclusion

Paracetamol-codeine preparations produce a significant increase in analgesia compared with paracetamol alone. This difference is comparatively small but on most measures, comparable with the effect of codeine versus placebo. Multidose studies show an increased incidence of side effects with paracetamol-codeine. Thus for occasional pain relief a paracetamol-codeine combination might be appropriate, but repeated use increases the occurrence of side effects.

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Appendix

APPLYING METHODOLOGICAL CRITERIA

- (A) Description of inclusion and exclusion criteria (5 points)
- (B) Equal distribution of relevant prognostic factors over treatment groups (5 points)
- (C) Randomisation performed (5 points); method of randomisation correct (5 points)
- (D) Loss to follow up: all randomised patients minus number of patients at main moment of effect divided by all randomised patients; loss to follow up less than 20% (5 points) or loss to follow up less than 10% (10 points)
- (E) Smallest group immediately after randomisation: 25-49 subjects (5 points) or 50-99 subjects (10 points) or 100 subjects or more (15 points)
- (F) Dosage schedule, timing of dosing (5 points)
- (G) Double blind design (20 points)
- (H) Relevant outcome measures (15 points)
- (I) Dosage considered adequate if less than 20% of subjects in paracetamol-codeine combination group receive rescue treatment at two hours of evaluation or if mean time to rescue treatment is less than two hours (5 points)
- (J) Report includes any form of side effects (5 points)
- (K) Presentation of results so that analysis can be checked; in case of semicontinuous or continuous variables presentation of mean or median with corresponding standard error or centile (5 points).

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Randomised, double blind, placebo controlled trial of penicillin V and amoxycillin in treatment of acute sinus infections in adults

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Abstract

Objective—To compare the effectiveness of penicillin V and amoxycillin with placebo in treatment of adult patients with acute sinusitis.

Design—Randomised, double blind, placebo controlled trial.

Setting—Norwegian general practice.

Subjects—130 adult patients with a clinical diagnosis of acute sinusitis confirmed by computed tomography.

Main outcome measures—Subjective status after three and 10 days of treatment, difference in clinical severity score between day 0 and day 10 as evaluated by the general practitioner, difference in score from computed tomography on day 0 and day 10, and duration of sinusitis.

Results—Amoxycillin and penicillin V led to significantly faster and better recovery than placebo. By day 10, 71 patients receiving antibiotic treatment (86%) considered themselves to be recovered or much better compared with 25 (57%) receiving placebo. The mean (95% confidence interval) reductions in clinical severity scores by day 10 were 5.4 (5.0 to 5.8) for penicillin V, 5.5 (4.9 to 6.0) for amoxycillin, and 3.4 (2.8 to 4.0) for placebo. For the antibiotic groups combined the number of patients with the greatest degree of improvement on computed tomography (scale 0-16)—that is, score 5-16 on day 10—was 31/83 (37%) compared with 10/44 (23%) receiving placebo. The median duration of the sinusitis was nine days in the amoxycillin group, 11 days in the

penicillin V group, and 17 days in the placebo group.

Conclusion—Penicillin V and amoxycillin are significantly more effective than placebo in the treatment of acute sinusitis.

Introduction

Acute sinusitis, an inflammation in the paranasal sinuses lasting no longer than one month, is a common clinical problem in general practice.¹⁻³ Acute sinusitis is a common reason for the prescription of antibiotics in adult patients.⁴

The effectiveness of antibiotic treatment, however, has been poorly documented. Only two placebo controlled, randomised studies with clinical findings and objective visualisation as inclusion criteria have been found in the literature, one in children⁵ and one in adults.⁶ The last study has met with criticism.⁷

Antibiotic treatment of acute sinusitis varies between countries.⁸⁻¹⁰ In Scandinavia penicillin V is the drug of choice.⁸ The most common bacteria in acute sinusitis are *Streptococcus pneumoniae* and *Haemophilus influenzae*, and the reason for using broad spectrum antibiotics is mainly the prevalence of *H influenzae*, which may have a low sensitivity to penicillin V.^{11 12}

Computed tomography of the paranasal sinuses has mainly been used in evaluating patients in need of nasal or sinus procedures and in staging patients with chronic sinusitis.^{13 14} Lately it has also been used in the diagnostic process of acute sinusitis,^{15 16} documenting involvement of several sinuses, mainly the maxillary and

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