Systematic overview of co-proxamol to assess analgesic effects of addition of dextropropoxyphene to paracetamol

A Li Wan Po, W Y Zhang

Abstract

Objective: To evaluate the comparative efficacy and tolerability of paracetamol-dextropropoxyphene combination and paracetamol through a systematic overview of randomised controlled trials.

Design: Systematic retrieval of trials of paracetamol-dextropropoxyphene, paracetamol, and placebo to allow pooling of results from head to head comparison trials and single active placebo controlled trials.

Subjects: 2231 patients with postsurgical pain, arthritis, and musculoskeletal pain reported in 26 randomised controlled trials.

Main outcome measures: Sum of difference in pain intensity; response rate ratio and difference in response rate with response defined as moderate to excellent pain relief; and rate ratio and rate difference of side effects.

Results: The difference in pain intensity between paracetamol-dextropropoxyphene and paracetamol was 7.3% (95% confidence interval -0.2 to 14.9). The response rate ratio for the combination and paracetamol was 1.05 (0.8 to 1.3) on the basis of the head to head trials. Indirect comparisons produced quantitatively consistent results. Compared with placebo, the combination produced more dizziness (3.1; 1.1 to 8.9) whereas paracetamol resulted in more drowsiness (1.8; 1.1 to 2.9).

Conclusion: On the basis of data on analgesic efficacy and acute safety in both head to head and indirect comparisons, there is little objective evidence to support prescribing a combination of paracetamol and dextropropoxyphene in preference to paracetamol alone in moderate pain such as that after surgery.

Introduction

Analgesic drug combinations are used widely both for self medication and as prescribed medication. In a recent survey of 30 teaching hospitals in the United Kingdom, combination products accounted for 73% of all paracetamol issues.¹ Co-proxamol, a combination product containing 650 mg paracetamol and 32.5 mg dextropropoxyphene hydrochloride, was the most popular prescription, accounting for 35%.¹ Such widespread use has attracted considerable controversy. Surprisingly, the debate to date has been based on quali-

tative assessments of the literature. Haigh, for example, claims that the combination of 1 g paracetamol and 30-60 mg codeine, instead of dihydrocodeine, given as separate tablets gives greater analgesia in acute pain, but he provides no supporting data.¹ In response, Sykes et al said that co-proxamol has been popular "perhaps because the combination does indeed work well, because it is generally well tolerated and because patients like it."² Cynics would point out that similar claims can be made for the use of tiger bones in rheumatic pain. To help to enlighten the debate we conducted a systematic overview of the relevant literature. Earlier meta-analyses have shown that while codeine may add to the analgesic efficacy of paracetamol, the additive effect is probably of no clinical significance at the currently used doses.^{3,4} We conducted a systematic review of the relevant randomised controlled trials to assess whether dextropropoxyphene adds to the analgesic effect of paracetamol.

Materials and methods

Retrieval of published studies

Reports of randomised controlled trials of paracetamol and dextropropoxyphene were identified through a systematic search consisting of electronic searching of Medline and BIDS (Embase and the Institute of Scientific Information (ISI) databases). The computerised searches covered the period 1966 to the end of March 1997. The same broad search strategy was used in both Medline and BIDS. A medical subject headings (MeSH) search in Medline was undertaken first, if possible, followed by a keyword search through both title and abstract. As Medline has standard terms (paracetamol entered as acetaminophen, dextropropoxyphene entered as propoxyphene) only one term was used. For BIDS, both terms were needed as keywords. We also conducted historical searches through the reference lists of reports retrieved through the electronic searches and review articles. Publications were retrieved as hard copies for subsequent study.

Inclusion and exclusion criteria

Only randomised controlled trials were included. Quality scoring of trials was restricted to this threshold criterion because of broad support on the critical importance of these items but less so on other items often included in quality scores. To facilitate interpretation, only studies including evaluations of

Centre for Evidence Based Pharmacotherapy, Department of Pharmaceutical Sciences, University of Nottingham, Nottingham NG7 2RD

A Li Wan Po, professor of clinical pharmacetics
W Y Zhang, research fellow

Correspondence to: Professor Li Wan Po

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conventional oral formulations of paracetamol and dextropropoxyphene hydrochloride or dextropropoxyphene napsylate were included in the meta-analysis. Formulations intended for administration by non-oral routes were excluded from the meta-analysis. A randomised study was defined in our inclusion criteria as one in which the investigators reported it as being randomised without necessarily defining the randomisation method explicitly. If a clearly non-random method (for example, dates of birth or sequential assignment) was used, however, then our protocol would have led to rejection of the trial concerned for the main analysis, although it would have been included in our sensitivity analysis. No trial fell in this category.

Data extraction

Data extraction was undertaken by two authors independently. Any disagreement was solved by discussion. A customised form was used to record the authors of the study, the year of publication, study design (double blind or single blind, crossover or parallel), type of pain (dental, postpartum, other surgical), dose regimen, population characteristics (age, weight, baseline pain intensity, sample size, etc), and outcomes (pain relief, pain intensity, remedication). In addition, we recorded the proportion of patients reporting any side effect, nausea, vomiting, stomach ache, dizziness, drowsiness, and headache.

Statistical analysis

The sum of pain intensity difference is a widely used outcome in the assessment of analgesics. Patients are asked to grade their pain intensity on a scale such as 0 to 3 at time intervals, and the difference in pain intensity relative to time zero or immediately before drug administration is calculated. The differences in pain intensity so calculated at different time points are summed to give the sum of the pain intensity difference (SPID). We adjusted this figure as previously described to account for differences in the scale anchors by using the equation shown:

$$\text{SPID}\% = (\text{SPID} / (\text{maximum score} - \text{minimum score}) \times n) \times 100$$

where the maximum and minimum pain intensity scores are from the relevant scales.^{4 5}

Standard errors were abstracted from the individual studies if provided. When the SEs or SDs and sample sizes were not provided or could not be calculated on the basis of the data reported, the pooled interstudy SE from studies reporting variances was used. All SEs were expressed in terms of units consistent with the outcome measures—that is, the percentage sum of the pain intensity difference.

The difference in effect (d_i) between the treatment and placebo or two treatments was derived as previously described.⁴ Pooled SDs between the treatment and placebo or two treatments were calculated first, and the SE of the difference was obtained from this pooled estimate. The inverse of the squared SE (sampling variance) of the difference in response was used as the weight (w_i). For estimating the weighted pooled difference in effect (d), the method previously described was used.⁴

Efficacy was also estimated with the response rate ratio (ResRR), defined as the proportion of patients

reporting moderate to excellent or greater than 50% pain relief during the observation period in the treatment group relative to the control group. Adverse effects were estimated with rate ratio (or relative risk) and rate difference in terms of any side effect, nausea, vomiting, dizziness, drowsiness, etc. In all cases, Rothman's method was used for interval estimation of the individual rate ratio and rate difference.⁶

In the pooling of relative risk and rate difference, the method of DerSimonian and Laird⁷ as implemented by Whitehead and Whitehead⁸ was used. The number needed to treat was estimated from the pooled rate difference.⁹ A random effects model was used if trials were heterogeneous on the basis of the Q statistic for heterogeneity.^{7 8} Results of both fixed and random effects modelling are shown when appropriate in the tables and graphs.

Paracetamol and the paracetamol-dextropropoxyphene combination were compared in two ways: firstly, indirectly, by estimating the pooled effects of paracetamol against placebo and the combination against placebo, and then comparing the two estimates; and, secondly, directly, by using the head to head comparisons without reference to the placebo group, even if provided.

In pooling the studies we considered the terms propoxyphene and dextropropoxyphene as equivalent, as only the dextro isomer of the analgesic is in clinical use. The salt forms, hydrochloride and napsylate, were assumed to have no effect on the systemic activity of the analgesic, and a dose of 65 mg of the hydrochloride was assumed to be equivalent to 100 mg of the napsylate, as previously described by Beaver.¹⁰

For each of the studies we calculated a standardised baseline pain score index (BPS%) to enable an comparison between trials of the mean severity of pain of the patients at entry. This was calculated by taking the mean baseline score reported in any given trial divided by the maximum score possible on the scale used. For example, if the scale used had a maximum score of 3 and the baseline score was 2 then the baseline score index was 67%. This adjusted for the different values used for anchoring the scales which were consistent at a descriptive level: no pain = 0% to severe pain = 100%.

Results

Characteristics of eligible trials

We retrieved 26 eligible trials.^{11–36} Six trials were three-armed, head to head comparisons of paracetamol-dextropropoxyphene, paracetamol, and placebo (table 1)^{11–16}; 21 trials were two-armed, placebo controlled trials, 15 of which compared paracetamol with placebo.^{17–30} The six other trials compared the paracetamol-dextropropoxyphene combination against placebo (table 2).^{31–36} One of the reports included two paracetamol versus placebo trials.¹⁸ Two of the three-armed trials included 1000 mg paracetamol as a comparator.^{13 14} That arm was excluded from both studies. Except for two trials^{16 31} all trials were single dose comparisons (tables 1 and 2). Data from the two multidose trials were included in sensitivity analyses of adverse effects. One report included no quantitative efficacy data at all.³¹ Another study reported efficacy in terms of pain score and pain relief in per cent per day, but in the author's description it was said

that patients were not instructed to keep track in any particular way.¹⁶ Not all the trials reporting values for the sum of the pain intensity difference also reported response rates for efficacy. Therefore, to obtain the pooled estimates the trials included in the different analyses do not necessarily match.

Of the four abstracts identified,^{37–40} three were from the same author. We did not pursue the authors for the raw data because all the reports were at least 10 years old. One trial published in German⁴¹ and one published in French⁴² were also identified. The German trial included paracetamol but only at a dose of 1000 mg, outside the focus of our study. The French trial evaluated efficacy of the analgesics in pain induced by voluntary interruption of pregnancy by mefepristone, and was

considered not appropriate for combination with studies of the types of pain considered in this review.

Quality of trials

Our inclusion criteria ensured that all the trials included in our pooled estimates of effect were protected from the major threats to interval validity. The trials were all randomised, controlled, and double blinded, and we could not see any obvious threats to these in the reports, although we adopted a permissive stance with respect to randomisation by assuming efficient randomisation even if the authors did not describe the randomisation scheme in detail. Most trials failed to report variance of the sum of the differences in pain intensity associated with the responses

Table 1 Characteristics of randomised controlled trials: three-armed, head to head with active and placebo controls

First author of trial	Design	Type of pain	Par-dxp (mg)	Para-cetamol (mg)	Period (hours)	Mean age (years)	Mean weight (kg)	BPS %	No of subjects			Sum of difference in pain intensity (SE)			No with moderate to excellent pain relief		
									Par-dxp (n=232)	Para-cetamol (n=229)	Placebo (n=229)	Par-dxp	Para-cetamol	Placebo	Par-dxp (n=237)	Para-cetamol (n=237)	Placebo (n=237)
Cooper ¹¹	DB-P	3rd molar extraction	650+100	650	4	23.5	62.4	76	42	37	37	3.6	2.8	0.1	23	20	6
Hopkinson ¹²	DB-P	Episiotomy	650+65	650	4	26.1	NR	58	50	50	50	5.4	4.4	3.1	36	34	21
Hopkinson ¹³	DB-P	Postpartum	650+100	1000*	4	24.6	66.7	70	74	75	75	5.1	6.6	2.6	60	64	50
Huskisson ¹⁴	DB-C	Arthritis	650+65F	1000*	6	NR	NR	NR	23	23	23	NR	NR	NR	NR	NR	NR
Liashek ¹⁵	DB-P	3rd molar extraction	650+100	650	4	18.3	71.5	NR	11	12	12	3.1 (1.2)	-0.5 (1.4)	-2.3 (1.0)	NR	NR	NR
Messick ¹⁶	DB-C	Musculoskeletal disorders	650+100	650	48†	NR	NR	NR	32	32	32	NR	NR	NR	NR	NR	NR

NR=not reported

Par-dxp=paracetamol-dextropropoxyphene; DB-P=double blind, parallel trial; DB-C=double blind, cross over trial; BPS%=percentage of baseline pain score relative to maximum pain score on scale 0%=no pain, 50%=moderate pain, 100%=severe pain.

*Excluded from analysis because of 1000 mg dose of paracetamol.

†Multidose studies excluded from pooling.

Table 2 Characteristics of randomised controlled trials: two-armed placebo controlled trials

First author of trial	Design	Type of pain	Paracetamol (mg)	Dxp (mg)	Period (hours)	Mean age (years)	Mean weight (kg)	BPS%	No of subjects		Sum of difference in pain intensity (SE)		No with moderate to excellent pain relief	
									Treatment	Placebo	Treatment	Placebo	Treatment	Placebo
Paracetamol v placebo									(n=585)	(n=559)			(n=109)	(n=47)
Bloomfield ¹⁷	DB-P	Postpartum	650	0	6	NR	NR	NR	22	26	10.8 (0.6)	8.4 (0.6)	NR	NR
Cooper ¹⁸	DB-P	Tooth removal	650	0	6	23.7	62.5	77	39	35	2.4	0.3	NR	NR
Cooper ¹⁸	DB-P	Tooth removal	650	0	4	31.9	70.7	73	49	43	3.4	2.1	NR	NR
Cooper ¹⁹	DB-P	Tooth removal	650	0	6	23.6	64.6	87	37	44	2.4	1.9	12	6
Dionne ²⁰	DB-P	3rd Molar extraction	650	0	6	28.9	68.6	NR	27	25	NR	NR	NR	NR
Forbes ²¹	DB-P	Postsurgical	650	0	6	39.2	74.5	83	31	33	4.9	2.4	17	11
Forbes ²²	DB-P	3rd Molar extraction	650	0	6	21.8	67.2	82	39	36	1.1	0.2	20	4
Hopkinson ²³	DB-P	Episiotomy	650	0	4	NR	NR	NR	88	88	5.2	2.1	51	16
Jain ²⁴	DB-P	Postsurgical	650	0	6	29.2	71.8	80	30	32	5.4 (0.8)	4.1 (0.7)	NR	NR
Melzack ²⁵	DB-P	Episiotomy	650	0	6	NR	NR	NR	29	29	6.7	5.8	9	10
Sunshine ²⁶	DB-P	3rd Molar extraction	650	0	6	22.5	60.6	67	30	30	4.2	1.7	NR	NR
Sunshine ²⁷	DB-P	Episiotomy	650	0	6	25.8	60.1	NR	75	50	4.4	1.5	NR	NR
Sunshine ²⁸	DB-P	Caesarean	650	0	6	26.1	60.3	NR	48	48	6.7	6.2	NR	NR
Terrence ²⁹	DB-P	3rd Molar	650	0	4	27.4	NR	85	11	11	4.3	1.9	NR	NR
Young ³⁰	DB-P	Postsurgical	650	0	4	46.0	68.5	NR	30	29	4.1 (0.6)	4.6 (1.0)	NR	NR
Paracetamol plus dextropropoxyphene v placebo									(n=200)	(n=45)			(n=45)	(n=26)
Buck ³¹	DB-P	Episiotomy	650	65	48*	NR	NR	NR	19	19	NR	NR	NR	NR
Evans ³²	DB-P	Orthopaedic	650	65	4	42.2	67.8	NR	30	30	3.3 (0.6)	2.1 (0.4)	NR	NR
Forbes ³³	DB-P	Oral surgery	650	100	12	NR	NR	NR	29	28	4.9	1.4	NR	NR
Honig ³⁴	DB-P	Postsurgical	650	100	6	38.0	72.5	NR	50	48	3.4 (0.5)	1.4 (0.6)	28	17
Petti ³⁵	SB-P	Postsurgical	650	100	6	49.0	NR	NR	31	32	4.7 (0.7)	2.2 (0.6)	17	9
Sunshine ³⁶	DB-P	Caesarean	650	100	6	25.8	60.4	NR	41	40	6.7	4.2	NR	NR

NR=not reported

Dxp=dextropropoxyphene; DB-P=double blind, parallel trial; SB-P=single blind, parallel trial; BPS%=percentage of baseline pain score relative to maximum pain score on scale 0%=no pain, 50%=moderate pain, 100%=severe pain.

*Multidose studies excluded from pooling.

Fig 1 Mean (95% confidence interval) differences in percentage sum of differences in pain intensity between treatments

measured, necessitating variance imputation or sample size weighting when we pooled the data (see table 1).

Head to head comparisons

A total of 461 patients took part in six head to head, three armed trials with both active and placebo controls.¹¹⁻¹⁶ Two of these gave no data on the efficacy outcome measures in a form usable in our analysis.^{14, 16} Huskisson used pain relief scores and undertook multiple testing at six hourly time points over 6 hours and reported that at three of those time points co-proxamol was better than paracetamol 1000 mg but not at the other three.¹⁴ No variance estimates were given. Messick on the other hand only reported mean pain score per hour, again without variance estimates.¹⁶ The mean value reported (1.78 pain score units per hour for the combination, 1.89 for paracetamol 650 mg, and 1.81 for propoxyphene) suggested no sharp

differences. The reported mean pain relief scores in per cent per day were 40.9, 39.5, and 39.0, respectively, again suggesting no obvious differences in efficacy. These two trials were the only two crossover trials retrieved by us. The results from the parallel group trials included in our meta-analysis indicate that both formulations were more effective than placebo, but there was no statistical difference in their efficacies on the basis of either the percentage sum of the pain intensity difference (see fig 1) or response rate ratio (see fig 2).

Indirect comparisons

A total of 397 patients participated in the paracetamol-dextropropoxyphene versus placebo trials. Figure 1 shows that the combination was effective, as shown by a pooled difference in sum of pain intensity difference of 12.7% (95% confidence interval 9.2 to 16.2%). Use of a random effects model led to the same conclusion (mean effect of 13.5%; 8.8% to 18.2%).

Overall, 1144 patients were included in the paracetamol versus placebo trials. These included patients from both the two-armed and three-armed studies. The pooled mean difference in the percentage sum of pain intensity difference was 9.4% (6.9% to 11.9%) with a fixed effects model and 9.4% (6.6% to 12.2%) with a random effects model, again indicating that paracetamol is an effective analgesic on the basis of this outcome measure.

Comparison of the effects estimated from the paracetamol-dextropropoxyphene versus placebo and the paracetamol versus placebo percentage sum of pain intensity difference (indirect estimation) failed to show any significant difference, as shown by the overlap of two sets of pooled confidence intervals (fig 1).

Use of the rate ratio of patients responding with moderate to excellent pain relief as a measure of efficacy yielded results consistent with the data on percentage sum of pain intensity difference. Both paracetamol and the paracetamol-dextropropoxyphene combination were more effective than placebo. There was no significant difference between the two paracetamol formulations, however, as shown by the overlap of two sets of pooled confidence intervals (fig 2). The random effects estimates should be used because of the heterogeneity of effects in the paracetamol versus placebo trials. Rate differences were 0.27 (0.17 to 0.38) for paracetamol and 0.24 (0.16 to 0.32) for paracetamol-dextropropoxyphene. A mean number needed to treat of 4 was obtained for both formulations by taking the inverse of rate difference in both cases. Compared with placebo, four subjects will on average require to be treated with either paracetamol or the combination for one more patient to obtain moderate to excellent pain relief.

Adverse effects

Comparison of side effect profiles showed that the combination of paracetamol and dextropropoxyphene caused more dizziness than placebo. On average, treating 42 patients will lead to one more patient complaining of dizziness than if they were receiving placebo. Surprisingly, paracetamol caused more drowsiness than placebo, an observation which clearly needs further confirmation because of its poor face validity. There was no difference in any of the reported side

Fig 2 Mean (95% confidence interval) rate ratios for moderate to excellent pain relief between treatments

effects between paracetamol and its combination with dextropropoxyphene (table 3).

Sensitivity analysis for indirect comparison

Direct versus indirect comparisons—Two estimates of paracetamol-placebo effect were derived, one on the basis of the results of the head to head trials including a placebo arm and the other based on placebo controlled trials not including a paracetamol-dextropropoxyphene

arm. This sensitivity analysis showed no difference in estimates of effect for placebo controlled trials in the two-armed studies (8.8%; 6.1% to 11.5%) when compared with the three-armed studies (14.1%; 6.9% to 21.4%). Similarly, for the combination product the estimated effect relative to placebo was no different in the two-armed studies (10.1%; 6.0% to 14.3%) than in the three-armed studies (19.3%; 12.8% to 25.9%). Both sets of trials therefore gave qualitatively consistent estimates (table 4), although the data suggest a more pronounced effect in the latter.

Method of analysis—Given that many of the studies considered in our meta-analysis failed to report on the variances associated with the estimates of effect, we undertook sensitivity analyses with respect to method of pooling. Firstly, we included only studies with variance estimates. Secondly, we used sample size weighting adopted by Eisenberg et al in their meta-analysis of non-steroidal anti-inflammatory drugs in cancer pain.⁵ Thirdly, we used imputation of variance, whereby we assigned the pooled estimate of variance, calculated from studies reporting such values, to estimate variance for the 19 studies that had not done so (tables 1 and 2). Pooling only studies reporting variance showed that in the indirect comparisons the estimated effect size for paracetamol relative to placebo was 8.3% (2.7% to 13.9%) while for the combination analgesic the corresponding value was 9.4% (6.9% to 12.5%). These results show no difference in effect between paracetamol and the paracetamol-dextropropoxyphene combination. The head to head studies were not numerous enough for this sensitivity analysis. Use of sample size as weight provided pooled estimates of effect which were consistent with those seen when variance in studies not reporting them were imputed by using the pooled estimate of variance from studies that had, as shown in table 5. Irrespective of the method for imputing variance, paracetamol and paracetamol-dextropropoxyphene were both more effective than placebo, but there was no difference in their effectiveness.

Discussion

Our meta-analysis supports the claim of Sykes et al that paracetamol-dextropropoxyphene is effective as an analgesic.² Implicit in their response to Haigh's

Table 3 Comparison of risk of side effects (95% confidence intervals) with paracetamol, paracetamol plus dextropropoxyphene, and placebo

Comparisons	Any side effect	Nausea	Dizziness	Drowsiness	Headache
Paracetamol plus dextropropoxyphene v paracetamol					
Crude rate	16/117 v 25/112	10/234 v 8/229	7/234 v 6/229	10/229 v 12/229	1/234 v 5 / 229
Weighted relative risk	0.62 (0.35 to 1.10)	1.16 (0.47 to 2.85)	1.11 (0.37 to 3.36)	1.04 (0.40 to 2.69)	0.30 (0.05 to 1.93)
Weighted risk difference	-0.08 (-0.18 to 0.02)	0.007 (-0.03 to 0.04)	0.01 (-0.02 to 0.04)	-0.06 (-0.24 to 0.12)	-0.01 (-0.03 to 0.004)
Paracetamol v placebo					
Crude rate	64/345 v 48/355	16/355 v 14/362	11/364 v 9/372	43/ 378 v 24/389	13/427 v 17/431
Weighted relative risk	1.42 (1.01 to 2.02)*	1.14 (0.54 to 2.40)	1.24 (0.47 to 3.26)	1.77 (1.10 to 2.86)*	0.79 (0.38 to 1.67)
Weighted risk difference	0.02 (-0.03 to 0.06)	0.003 (-0.03 to 0.03)	0.002 (-0.02 to 0.02)	0.02 (-0.01 to 0.05)	-0.01 (-0.03 to 0.01)
Paracetamol plus dextropropoxyphene v placebo					
Crude rate	24/167 v 28/239	13/295 v 10/367	14/316 v 5/388	15/279 v 10/356	7/295 v 18/367
Weighted relative risk	1.16 (0.69 to 1.97)	1.65 (0.73 to 3.69)	3.09 (1.07 to 8.87)*	1.69 (0.76 to 3.74)	0.70 (0.29 to 1.68)
Weighted risk difference	0.02 (-0.05 to 0.09)	0.02 (-0.01 to 0.05)	0.02 (0.0001 to 0.046)*†	0.02 (-0.01 to 0.05)	-0.03 (-0.06 to -0.01)*‡

*P≤0.05.

†Number needed to treat was 43 (21 to 6940).

‡Number needed to treat was -30 (-138 to -17) (favours paracetamol plus dextropropoxyphene—that is, fewer headaches in the active treatment group).

Table 4 Sensitivity analysis (95% confidence interval) with respect to type of placebo controlled trials

Type of trial	Difference in SPID%	Response rate ratio*
Paracetamol v placebo		
Placebo trials in two armed studies	8.8 (6.1 to 11.5)	2.2 (1.6 to 3.0)
Placebo trials in three armed studies	14.1 (6.9 to 21.4)	1.9 (1.3 to 2.6)
Overall	9.4 (6.9 to 11.9)	2.1 (1.5 to 3.1)
Paracetamol plus dextropropoxyphene v placebo		
Placebo trials in two armed studies	10.1 (96.0 to 14.3)	1.7 (1.2 to 2.5)
Placebo trials in three armed studies	19.3 (12.8 to 25.9)	1.7 (1.1 to 2.6)
Overall	12.7 (9.2 to 16.2)	1.4 (1.2 to 1.7)

SPID=sum of pain intensity difference.

*Response rate ratio for patients receiving treatment relative to placebo. Response rate is defined as proportion of patients reporting moderate to excellent or more than 50% pain relief during observation.

Table 5 Sensitivity analysis with respect to method of variance imputation for difference in SPID% (95% confidence interval)

Detail	Pooled estimate weighted for sample size*	Pooled estimate weighted for variance†
Paracetamol v placebo (n=17)	7.9 (4.2 to 11.7)	9.4 (6.9 to 11.9)
Paracetamol plus dextropropoxyphene v placebo (n=9)	11.4 (6.8 to 16.0)	12.7 (9.2 to 16.2)
Paracetamol plus dextropropoxyphene v paracetamol (n=3)	5.3 (-2.7 to 13.2)	7.3 (-0.2 to 14.9)

SPID=sum of pain intensity difference.

*Mean difference in SPID% weighted for sample size as described by Eisenberg et al.⁵

†Mean difference in SPID% weighted for variance, with variance in studies not reporting them imputed by using pooled estimate from studies reporting variance.

criticism of the widespread use of paracetamol-dextropropoxyphene¹ was the assumption that the combination was more effective than paracetamol alone. Our systematic overview shows that the current data do not support this view. Happily, though, the incidence of adverse effects is no higher with the combination than with paracetamol alone. Single dose randomised controlled trials cannot be expected to capture estimates of potential for abuse, however, and this is a subject of concern with combination products containing centrally acting analgesics.⁴³

In undertaking our meta-analysis, we were hampered by the absence of variance estimates in many of the trials. This is a problem which should decrease with the wider adoption of the CONSORT statement on the quality of reporting of clinical trials.⁴⁴ The fact that irrespective of the method of variance imputation the same qualitative results were obtained gives us some confidence with respect to the robustness of our conclusion; on current evidence, the combination of dextropropoxyphene 65/100 mg with paracetamol 650 mg is no better than paracetamol 650 mg on its own for the type of pain considered in this meta-analysis.

There were relatively few studies, and it is possible that we could have missed small additive analgesic effects of dextropropoxyphene. Our 95% confidence interval estimates suggest that the magnitude of effect observed is neither statistically nor clinically meaningful. The differences in effect between the combination and paracetamol in the head to head studies were 7.3% (-0.2% to 14.9%) on the basis of the percentage sum of differences in pain intensity and 1.1 (0.8 to 1.3) on the basis of response rate ratio. In an earlier communication we provided data to suggest that an analgesic effect, of 7 (3 to 10) assessed by using percentage sum of differences in pain intensity, was not translated into an increased number of patients who obtained at least moderate pain relief.⁴ While that study assessed the possible additive effect of different drugs (codeine and caffeine rather

Key messages

- Combinations of paracetamol with centrally acting analgesics are widely used, accounting for 73% of all prescriptions for paracetamol in a recent hospital survey in the United Kingdom
- The combination of paracetamol (650 mg) with dextropropoxyphene hydrochloride (32.5 mg) is particularly popular
- In both head to head and indirect comparisons of paracetamol and the combination, the combination was no better than paracetamol on its own
- Since the total number of patients in the few published head to head comparisons was modest, small differences in effect cannot be excluded but these are unlikely to be of clinical importance

than dextropropoxyphene), the fact that all three drugs are centrally active and that the same measure (percentage sum of pain intensity difference) was used suggests that comparison of the two sets of results is reasonable.

To explain why discordant conclusions may be obtained when relative efficacy and response rate ratio are used as outcomes, we propose that although a patient may well perceive a difference in pain intensity, this change may not be sufficient to be judged important. In other words, a decrease in pain intensity, reflected in the percentage sum of pain intensity difference, may not be sufficient for the patient to classify this change as a categorical change—for example, from severe to mild and reflected in response rate ratio as an outcome measure.

It has been suggested that as dextropropoxyphene is subject to a high first pass metabolism⁴⁵ single dose studies are inadequate to estimate the efficacy of the drug. In the only two multiple dose studies we could identify a beneficial effect over and above that of paracetamol was not detected.^{16,31} We concur with the view of Miller et al that the popularity of the paracetamol combination does not lie in improved efficacy.⁴⁶

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Clinical and angiographic predictors of stroke and death from carotid endarterectomy: systematic review

P M Rothwell, J Slattery, C P Warlow

Abstract

Objective: To identify risk factors for operative stroke and death from carotid endarterectomy.

Design: Systematic review of all studies published since 1980 which related risk of stroke and death to various preoperative clinical and angiographic characteristics, including unpublished data on 1729 patients from the European carotid surgery trial.

Main outcome measure: Operative risk of stroke and death.

Results: Thirty six published studies fulfilled our criteria. The effect of 14 potential risk factors was examined. The odds of stroke and death were decreased in patients with ocular ischaemia alone (amaurosis fugax or retinal artery occlusion) compared with those with cerebral transient ischaemic attack or stroke (seven studies; odds ratio 0.49; 95% confidence interval 0.37 to 0.66;

$P < 0.00001$). The odds were increased in women (seven studies; 1.44; 1.14 to 1.83; $P < 0.005$), subjects aged ≥ 75 years (10 studies; 1.36; 1.09 to 1.71; $P < 0.01$), and with systolic blood pressure > 180 mm Hg (four studies; 1.82; 1.37 to 2.41; $P < 0.0001$), peripheral vascular disease (one study; 2.19; 1.40 to 3.60; $P < 0.0005$), occlusion of the contralateral internal carotid artery (14 studies; 1.91; 1.35 to 2.69; $P < 0.0001$), stenosis of the ipsilateral internal carotid siphon (five studies; 1.56; 1.03 to 2.36; $P = 0.02$), and stenosis of the ipsilateral external carotid artery (one study; 1.61; 1.05 to 2.47; $P = 0.03$). Operative risk was not significantly related to presentation with cerebral transient ischaemic attack versus stroke, diabetes, angina, recent myocardial infarction, current cigarette smoking, or plaque surface irregularity at angiography. Multiple regression analysis of data from the European carotid surgery trial identified cerebral versus ocular events at

Department of Clinical Neurosciences, Western General Hospital, Edinburgh, EH4 2XU

P M Rothwell, research fellow
J Slattery, statistician
C P Warlow, professor of neurology

Correspondence to: Dr P M Rothwell, Department of Clinical Neurology, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE
peter.rothwell@cneuro.ox.ac.uk

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