Clinical rheumatology, 1989, **8**, N° 2 245-250

Treatment of fibromyalgia (Fibrositis syndrome): A parallel double blind trial with carisoprodol, paracetamol and caffeïne (Somadril comp®) versus placebo

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SUMMARY *Forty-three of fifty-eight (74.1%) female patients with fibromyalgia completed an eight-week treatment period testing the combination of carisoprodol, paracetamol (acetaminophen) and caffeine versus placebo. Twenty-three patients received placebo and twenty active medication. In the placebo group 56.5% of the patients used additional analgesics or nonsteroidal anti-inflammatory drugs compared to only 20% in the active treatment group ($p = 0.015$). Forty-three percent of the patients in the placebo group and none of the patients in the active treatment group used tricyclic antidepressants, anxiolytics or sedatives ($p = 0.0008$). Active treatment gave statistically significant improvement after treatment for pain ($p < 0.01$), for sleep quality ($p < 0.01$) and for the general feeling of sickness ($p < 0.05$). In the active treatment group increased pressure pain threshold after eight weeks was found at 70% of the sites measured, while the pressure pain threshold was increased at only 30% of the sites in the placebo group. In the placebo group improvement was found for the pain and sleep quality ($p < 0.05$). This improvement may in part be due to the large amounts of extra medication in this group. Thus, the combination of carisoprodol and paracetamol (acetaminophen) and caffeine are effective in the treatment of fibromyalgia.*

Key words: Fibromyalgia, Fibrositis, Pain, Carisoprodol, Paracetamol.

INTRODUCTION

In the last decade authors have focused on several aspects of fibromyalgia. Few controlled studies, however, have been performed in order to evaluate the efficacy of drug treatment in this soft tissue pain syndrome. Studies on the treatment of fibromyalgia with tricyclic antidepressants alone or in combination with other drugs have been published (1,2). It was found that the tricyclic antidepressants used had some therapeutic effects in fibromyalgia. In another study (3), it was found that corticosteroids had no therapeutic effects in fibromyalgia. It has been reported by Campbell et al. (4), that treatment with the tricyclic muscle relaxant, cyclobenzaprine, showed a therapeutic response in this syndrome.

Carisoprodol, N-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate, is chemically related to mephenesin and meprobamate and it is not only a muscle relaxant but also an analgesic (5). It is further reported (5) that pharmacologically, carisoprodol has a depressant action on the reticular formation,

Received 2 September 1988,
Revision-accepted 16 January 1989,
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but does not produce behavioural changes, in contrast to the effects of barbiturates and other hypnotics. It is suggested (5) that the analgesic action of carisoprodol affects the central nervous centres concerned with pain perception. Carisoprodol alone has been reported less effective in the treatment of fibromyalgia (6), but it has never been tested in combination with the analgesic paracetamol (acetaminophen). The effect of paracetamol on fibromyalgia has not been sufficiently studied. One might assume that consumption of paracetamol is relatively high among patients with fibromyalgia, at least in countries where it may be bought without a prescription. However, the efficacy of paracetamol-containing drugs in fibromyalgia, still remains an open question.

Based on the hypothesis that fibromyalgia might have both a peripheral and a central pain component, and on the fact that sleep disturbances may be involved in the pathogenesis of the syndrome (7), this study was designed as a parallel double-blind trial testing the combination of carisoprodol, paracetamol and caffeine (Somadril Comp®) versus placebo.

MATERIAL AND METHODS

Patients.

Fifty-eight female patients, with fibromyalgia according to Smythe (8) and Yunus (9), participated in the study. Forty-three patients, of whom 20 got active medication and 23 got placebo, completed the eight week treatment period. The mean age of all patients was 47.4 ± 1.8 years (mean ± SEM), range 25-67 years. Mean age in the active treatment group was 46.0 ± 2.6 (mean ± SEM), range 34-65 years and in the placebo group 48.3 ± 2.4 (mean ± SEM), range 25-67 years, $p > 0.05$). Duration of disease in the active treatment group was 20.8 ± 2.7 years (mean ± SEM), range 5-44 years; in the placebo group 17.6 ± 2.3 years (mean ± SEM), range 4-47 years, $p > 0.05$. Before the patients were admitted to the study, they went through a general medical investigation to rule out possible coexisting disorders. The patients were asked not to use any drugs with analgesic or sedative effect for 72 hours prior to the start of the study. No patients reported such use.

Pressure pain threshold.

Pressure pain threshold measurement was performed at preselected tender point sites at baseline and after eight weeks of treatment. The measurements were done using a dynamometer constructed for research purposes at Oslo Sanitets-forenings Rheumatism Hospital. The dynamometer can measure applied pressure in grams per centimeter square (cm^2). The manometer has a range from 400 to 4000 grams and a scale with 100 gram steps. This was connected to a ten centimeter round extension with a flat one cm^2round tip. No sharp edges could disturb the measurements.

Tender point selection.

Ten tender point sites were selected based on their most frequent locations as described by Travell and Simons (10). The following tender point sites were selected for pressure pain measurements: 1-2. The upper fold of right and left m.trapezius. 3-4. Right and left m. sternalis at the second costochondral junction.5-6. Proximal insertion of right and left m.supinator at the lateral epicondyle.7-8. Right and left trochanter major. 9-10. Right and left m.tibialis anterior, ten cm distally to the proximal insertion. The threshold measurements were performed and registered by the same person both at baseline and after eight weeks. Such measurements represent a point at which a sensation of pain is reported by the patient. It this study, this was chosen as the examiners mode of pain assessment.

Pharmacological compounds.

As pharmacologically active medication 2 tablets were given 3 times daily, each tablet containing carisoprodol 200 mg, paracetamol (acetaminophen) 160 mg and caffeine 32 mg. The addition of caffeine as an adjuvant has been found effective as it improves the analgesic effect (11) of paracetamol. Further, caffeine may counteract the drowsiness experienced by some patients.

Carisoprodol has a rapid absorption with maximum blood concentration after one hour and with a T 50 of 7 hours. Meprobamate is the main metabolite of carisoprodol. Paracetamol is rapidly absorbed and reaches maximum blood levels after 30 minutes. The T 50 takes between 2-3 hours. Caffeine has shown a great individual variation regarding absorption. The T 50 takes from 3-6 hours. As placebo tablets nonactive and nontoxic substances were given. There were no detectable difference between the placebo tablets and the tablets containing active compounds regarding color, form, size or taste.

Study design.

This study was an eight-week parallel doubleblind trial to evaluate the effect of carisoprodol, paracetamol and caffeine versus placebo in the treatment of fibromyalgia. The patients were randomly selected and each patient received one bottle containing either active medication (carisoprodol 200 mg, paracetamol 160 mg and caffeine 32 mg) or placebo. After the treatment was stopped all the remaining tablets were returned and counted. The patients were instructed to take their medication three times daily at approximately the same time.

Patients also received a 10 cm visual analog scale (VAS) for selfreporting. The parameters were pain, sleep and general feeling of sickness. The pain scale was defined as 0 = extremely painful and 10 = no pain at all. The sleep scale as 0 = awake all night and 10 = slept all night. The general feeling of sickness scale was defined as 0 = I feel as sick as possible and 10 = I don't feel sick at all. These scales had to be filled out each day and to be returned in a closed envelope at the end of each week. In addition the patients received a diary in which they were asked to report all extra medication taken during the study as well as any possible side effects. This was also to be reported daily and to be returned together with the visual analog scales. None of the envelopes were opened until the randomisation code was broken at the end of the study. Patient dropouts were defined as those who failed to return for the second visit after eight weeks. Extra medication sufficient to be registered as additional use, was at least one tablet daily for three consecutive days.

Statistics.

Differences between baseline and eight-week treatment measurements and differences between treatment groups were calculated with Wilcoxon rank sum test for paired and unpaired samples and Students t-test.

RESULTS

Forty-three of the fifty-eight (74.1%) patients completed the study of whom 23 patients received placebo medication while 20 received active compounds. The use of additional medication for pain relief was greater in the placebo treatment group than in the active treatment group. This was statistically significant, $p = 0.015$, (Table I). 43.5% of the patients in the placebo treatment group used tricyclic antidepressants, anxiolytics or sedatives while none of the patients in the active treatment group reported any use of such drugs during the eight week treatment period, $p = 0.0008$ (Table I). The total use of extra medication in the active treatment group was less than in the placebo treatment group ($p = 0.007$).

Table II shows the visual analogue scale scores for the active and the placebo treat-

Table I: *Extra medication reported by the patients during eight weeks of continuous treatment*

Patients	Analgesics Antiflogistics		Antidepressiva, Anxiolytics Sedatives	
	Active group	Placebo group	Active group	Placebo group
2 (3)	0	1	0	1
10 (4)	0	0	0	0
13 (6)	0	1	0	1
14 (11)	0	0	0	0
20 (12)	0	1	0	0
22 (18)	1	0	0	0
23 (19)	1	1	0	1
25 (21)	0	0	0	0
36 (29)	0	1	0	0
39 (31)	0	0	0	0
40 (32)	0	0	0	1
44 (41)	0	1	0	1
55 (45)	0	0	0	0
56 (46)	1	1	0	1
68 (50)	1	0	0	0
71 (57)	0	1	0	0
77 (61)	0	0	0	0
78 (62)	0	1	0	1
79 (70)	0	1	0	1
82 (72)	0	1	0	1
(80)		1		1
(83)		0		0
(84)		1		0
Total	4/20	13/23	0	10/23
Mann-Whitney test		p = 0.015		p = 0.0008

1 - Reported use of additional medication
0 - Report of no use of additional medication
In brackets - placebo patients

Table II: *Changes in pain, sleep and general feeling of sickness in patients with fibromyalgia during treatment*

	Active treatment (n = 20)			Placebo treatment (n = 23)		
VAS	0 Weeks	8 Weeks	P-value	0 Weeks	8 Weeks	P-value
Pain	3.2 ± 1.9	6.9 ± 1.3	$p < 0.01$	2.9 ± 2.1	5.3 ± 2.4	$p < 0.05$
Sleep quality	4.1 ± 2.4	7.4 ± 2.0	$p < 0.01$	3.4 ± 2.5	6.1 ± 2.6	$p < 0.05$
General feeling of sickness	4.5 ± 2.0	6.8 ± 1.3	$p < 0.05$	3.6 ± 2.8	6.8 ± 2.6	$p > 0.05$

Values shown are visual analog scale scores (Mean + SD) in cm, on a 10-cm line. For statistical analysis Wilcoxon rank sum test was used. P-values $\leqslant 0.05$ were considered significant.

ment groups after 8 weeks treatment. In the active treatment group statistically significant improvement was found for pain ($p < 0.01$), for sleep ($p < 0.01$) and for general feeling of sickness ($p < 0.05$). In the placebo group there was significant improvement for pain ($p < 0.05$) and sleep ($p < 0.05$), while no statistically significant improvement was found ($p > 0.05$) for the general feeling of sickness.

Table III shows the pressure pain thresholds at tender point sites at baseline and after

Table III: *Changes in pressure pain thresholds at selected tender point sites in patients with fibromyalgia during treatment*

	Active treatment (n = 19)			Placebo treatment (n = 21)		
	0 Weeks	8 Weeks	P-value	0 Weeks	8 Weeks	P-value
Right m trapezius	1300 ± 72.4	1642 ± 126.9	$p<0.03$	800 ± 100	950 ± 50	$p>0.05$
Left m trapezius	1325 ± 149.3	1550 ± 165.8	$p>0.05$	1060 ± 136.4	1480 ± 274.6	$p>0.05$
Right m. sternalis	861 ± 114.8	1310 ± 95.9	$p<0.005$	816 ± 79.2	1133 ± 105.4	$p<0.03$
Left m. sternalis	1044 ± 66.9	1355 ± 74.7	$p<0.004$	1041 ± 110.4	1266 ± 106.8	$p>0.05$
Right m. supinator	920 ± 72.7	1150 ± 83.3	$p<0.05$	971 ± 179.6	1342 ± 216.9	$p>0.05$
Left m. supinator	887 ± 109.3	1350 ± 203.5	$p=0.05$	922 ± 96.8	1255 ± 149.2	$p>0.05$
Right troch.	1533 ± 87.3	1734 ± 251.5	$p>0.05$	1650 ± 241.2	2150 ± 333.3	$p>0.05$
Left troch.	1380 ± 87.9	1910 ± 110	$p<0.0006$	1609 ± 254.9	1858 ± 357.3	$p>0.05$
Right m. tibialis ant.	1025 ± 70	1412 ± 107.6	$p<0.005$	1300 ± 200.4	1881 ± 249.3	$p>0.05$
Left m. tibialis ant.	1083 ± 70.3	1600 ± 187.9	$p<0.02$	1327 ± 204.1	1763 ± 257.7	$p>0.05$

Values are shown as gr/cm^2(Mean ± SEM). Statistical analysis with Students t-test.
P-values ≤ 0.05 were considered significant.

group statistically significantly augmented pressure pain thresholds were found at the right musculus trapezius ($p < 0.03$), the right ($p < 0.005$) and left ($p < 0.004$) musculus sternalis at the second costochondral joint level, the right ($p < 0.05$) and left ($p = 0.05$) musculus supinator at the lateral epicondyle, over the left trochanter ($p < 0.0006$) and over the right ($p < 0.005$) and left ($p < 0.02$) musculus tibialis anterior. In the placebo group statistically significantly augmented pressure pain threshold was only found at the right musculus sternalis ($p < 0.03$) No statistically significant improvement for pain, sleep or general feeling of sickness was found between the two groups ($p > 0.05$). No serious side effects were reported. An initial light drowsiness was reported in some cases not persisting for more than 3-4 days. Of the 58 patients who initially agreed to participate 15 dropped out. Two of 15 did not return the VAS and gave no reason for their noncompliance. Three of 15 dropped out due to lack of therapeutic effect. One of 15 decided not to participate as therapy was not required due to less pain than normal. The remaining 9 of 15 were excluded due to incomplete scoring of the VAS during the 8-week period of the study. Five patients completed 7 weeks, two completed 5 weeks, one completed 4 weeks and one completed 3 weeks.

DISCUSSION

The present data show that a combination of carisoprodol, paracetamol and caffeine has therapeutic effects in fibromyalgia. The patients in the active treatment group reported significant improvement for the general feeling of sickness which was not found in the placebo group. Improvement of the pressure pain thresholds was seen at more tender point sites in the active treatment group (70%) than in the placebo group (30%). Both in the active treatment group and the placebo group improvement of pain and sleep quality was observed. The improvement seen in the placebo group is most likely due to the large amount of extra medication used by these patients.

Tablets with 500 mg paracetamol were most frequently used as extramedication in the placebo group. One may expect that a total of at least 2000-3000 mg of paracetamol a day would be needed to obtain analgesic effect. Thus, the small amount of paracetamol (a total of 960 mg daily) used in the active treatment group was probably too little to relieve fibromyalgic pain alone. The therapeutic effect in the active treatment group is therefore probably achieved by the combination of paracetamol, carisoprodol and caffeine.

The sedative effect of carisoprodol, may augment the analgesic effect of paracetamol by decreasing the state of tension induced by the chronic pain. It cannot be excluded that carisoprodol, known to act directly on the reticular formation (5) in the brain stem, may influence the modulation of pain impulses in these centres. Thus, it is possible that carisoprodol in some way may decrease the perception of pain.

The use of caffeine as an adjuvant has been described in a previous study (11) where it was found that a combination of paracetamol (acetaminophen) with caffeine was more effective than paracetamol alone. It was also found (11) that a combination of 65 mg caffeine with 500 mg paracetamol, effectively relieved pain in pain patients. The pharmacological effects of caffeine (11) include potentiation of the effects of prostaglandin synthesis inhibitors and inhibition of histamine release from mastcells. The latter effect implies that caffeine can antagonize one of the effects of substance P, namely the release of histamine from mastcells. Substance P CSF levels in fibromyalgia have been found elevated (12) and may in some way be involved in the pathogenesis of the disease in causing sensitization and hyperalgesia.

In conclusion, the present data show that the combination of carisoprodol, paracetamol (acetaminophen) and caffeine has a therapeutic effect in fibromyalgia. The treatment increased the pressure pain thresholds at tender points and relieved pain and the sleeping problems seen in this syndrome.

Acknowledgements: H.V. thanks Paal Kristiansen for valuable assistance in the work of preparing all the data. Further thanks to the personnel of Dumex Ltd., Norway for technical assistance.

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