

The treatment of arthritis with a lipid extract of *Perna canaliculus*: a randomized trial

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SUMMARY. Objective: to assess the efficacy of a lipid extract of the New Zealand green-lipped mussel, *Perna canaliculus* in rheumatoid and osteoarthritis and compare it with green-lipped mussel powder. Design: A double-blind 3-month parallel comparison of the two preparations and a further 3-month period on lipid extract for all patients. Setting: The out-patient department of the Glasgow Homoeopathic Hospital. Interventions: Stabilized green-lipped mussel powder, 1150 mg/day and the derived lipid extract, 210 mg/day. Main Outcome Measures: Articular index of joint tenderness (AI), morning stiffness (limbering-up-time, LUT), grip strength in each hand, visual analogue scale of pain (VA) and functional index (FI). Results: Seventy six percent of rheumatoid and 70% of osteoarthritic patients benefitted. AI, LUT and FI improved significantly by 3 months. The two preparations appeared equally efficacious. One patient experienced fluid retention and one developed nausea. There were no other adverse reactions. Conclusion: Both the stabilized freeze-dried mussel powder and its derived lipid extract are effective in reducing pain, swelling and stiffness and in improving functional index in rheumatoid arthritis and osteoarthritis.

INTRODUCTION

About 20 years ago we became aware of the therapeutic possibilities of a freeze-dried preparation of the New Zealand green-lipped mussel, *Perna canaliculus*. An open 4-year study in patients who had failed to respond to first line therapy and homoeopathy, showed that it was beneficial in both rheumatoid arthritis and osteoarthritis, and a double-blind placebo-controlled trial confirmed that it could be of benefit to 68% of patients suffering from rheumatoid arthritis and 40% of those suffering from osteoarthritis.¹ Improvements were seen in the amount of pain experienced, the degree of morning stiffness, the functional ability and night pain.

Since then, other studies have been carried out, some of which confirmed our original findings while others did not.²⁻⁵ This suggested a possible variation in the quality of the material used. Research in Australia and Japan proved that the then currently available freeze-dried powder was unstable and a stabilization process to protect the activity was developed and patented by Biomex Australia. The material thus produced was subsequently used to prepare a lipid extract from the mussel powder.

This mussel powder should not be confused with any of the currently available mussel powder products sold in the UK and Europe, including those produced by McFarlane New Zealand under the brand name 'Seatone'.

One of the problems with a shell-fish preparation is the possibility of allergy. It was partly to overcome this, and partly because the N-3 essential fatty acids are present in the oily portion of the mussel rather than in the protein fraction, that the lipid extract was developed. This has been shown to have anti-inflammatory activity in rats,⁶⁻⁹ in vitro effects on leucotriene biosynthesis in human polymorphonuclear leucocytes and on prostaglandin production in human monocytes.¹⁰ The present study was designed to determine whether the clinical efficacy of the lipid fraction was equal to that of the whole freeze-dried preparation in patients with rheumatoid arthritis and osteoarthritis. Since the original study was a double-blind, placebo-controlled assessment of the green-lipped mussel powder, which suggested its efficacy, the West Ethical Committee agreed that a further placebo arm was unnecessary. The present study is therefore a double-blind comparison of the Biomex stabilized mussel powder and

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its derived lipid extract. Two questions were asked: was the lipid extract clinically effective? and was there any difference between the two preparations?

PATIENTS AND METHODS

Sixty new referrals to the out-patient department of the Glasgow Homoeopathic Hospital, were invited to take part in the trial, 30 patients with classical rheumatoid arthritis¹¹ and 30 with clinical and radiological evidence of osteoarthritis. Calculations based on the results of the double-blind trial suggested that 7–10 patients per group would be sufficient to demonstrate a 50% reduction in symptoms with 95% confidence. Fifteen patients per group was therefore considered adequate.

Inclusion criteria for the rheumatoid patients required that they fulfilled the 1958 diagnostic criteria for classical rheumatoid arthritis¹¹ while the osteoarthritic patients required radiological evidence of osteoarthritis in addition to the symptoms and signs. Exclusion criteria included other concomitant chronic disorders, pregnancy and living too far from Glasgow for easy travel. In this study no patient was excluded because he or she was on second line drugs. This had been an exclusion criterion in the previous study. Fifteen of those with rheumatoid arthritis were on second line drugs. Apart from one patient who had discontinued all anti-inflammatory drugs prior to being seen at the Homoeopathic Hospital, the others were on standard NSAIDs. All but three of the osteoarthritic patients were also on standard NSAIDs.

The 30 patients in each category were randomly assigned to either Group A, the lipid fraction, or Group B, the stabilized mussel powder. Randomization was achieved by means of equal numbers of A and B slips placed in envelopes labelled either rheumatoid arthritis or osteoarthritis. Slips were drawn blindly from the appropriate envelope to allocate patients to either A or B on entry to the trial. Neither the patients nor the physician assessing the results, knew which preparation was given. The capsules and instructions as to dose (five capsules, 1150 mg/day for the mussel powder, and three capsules, 210 mg/day for the lipid extract) were given to the patients by the hospital pharmacy staff who carried out the random assignment and kept the code, but who did not know which preparation was A and which was B. All previous therapy was left unaltered and no other treatment was given at the hospital throughout the 6 months of the trial. This approach was identical to that used in the original trial.

The double-blind section of the trial was continued for 3 months, after which all patients were given the lipid extract for a further 3 months. The assessing physician did not know who changed treatments. The code was not broken until all the patients had completed the 6 months of the trial.

Progress was monitored by means of the articular index (AI),¹² morning stiffness (limbering up time LUT), grip strength in each hand,¹³ pain as assessed by the visual analogue scale (VA),^{14,15} functional index (FI)¹⁶ and the presence or absence of night pain. Any side-effects were noted.

Blood was taken for full blood counts and erythrocyte sedimentation rate (ESR) and rheumatoid factor in the case of rheumatoid patients, at the beginning and end of the trial. At 3 months and again at 6 months, both the patient and the assessing physician made their own assessments of whether there had been improvement or not. Patients who had both preparations were asked to give their assessments of relative efficacy and ease of use at the end of the trial.

The results were analysed by means of the Wilcoxon matched-pairs, signed-ranks test and the Mann Whitney U test.¹⁷ Non-parametric statistics were chosen because of the skewed nature of the data.

Both the stabilized mussel powder and the lipid extract were supplied by Biomex, Surrey Hills, Victoria, Australia. Ethical approval was obtained from the West Ethical Committee, West Glasgow Hospitals University NHS Trust.

RESULTS

Fifteen patients were assigned to each of the four groups and baseline comparability was good (Table 1).

One patient dropped out from rheumatoid Group A, and two patients dropped out from each of the two osteoarthritic groups. The rheumatoid patient experienced a transient exacerbation of fluid retention and withdrew from the trial. The four osteoarthritic patients dropped out because of transport difficulties.

Apart from the one case of fluid retention (which occurred on the lipid extract) one patient had marked nausea with the stabilized mussel powder, but no upset with the lipid preparation. There were no other adverse effects from either preparation. Two patients discovered that after 1 month on the lipid extract they could reduce the dose to one capsule daily with continuing benefit, which is in keeping with previous experience that many patients can reduce their dosage.

Rheumatoid arthritis

In the rheumatoid patients, significant improvements were obtained in articular index, morning stiffness and functional index in both groups A and B in the double-blind portion of the study (Tables 2 & 4). The visual analogue scale of pain did not improve significantly in either group although there were some marked individual improvements. Some patients experienced marked improvements in grip

Table 1 Sex distribution and mean age and duration of disease in the 60 patients

	M:F	Age (years)	Duration of disease (years)
Rheumatoid patients			
Group A	1:14	46.8	7.1
Group B	1:14	47.1	10.0
Osteoarthritic patients			
Group A	5:10	57.3	10.4
Group B	3:12	52.8	12.5

Table 2 Mean parameters (with SD) in the rheumatoid patients at base line and after 1 and 3 months of treatment

	AI	LUT	Grip strength		VA	FI
			Right	Left		
Group A						
Base line	14.8 (8.2)	98.4 (148.3)	123.9 (67.1)	117.5 (45.5)	6.6 (1.3)	15.6 (6.7)
1 month	8.1 (6.8)	46.3 (54.0)	143.2 (86.2)	158.9 (85.5)	4.9 (2.1)	11.2 (8.8)
3 months	5.9 (7.3)	27.1 (33.3)	154.6 (81.3)	158.9 (71.4)	4.7 (3.1)	8.9 (8.3)
Group B						
Base line	12.9 (7.8)	69.7 (90.2)	142.0 (57.1)	136.0 (74.7)	5.9 (1.8)	12.9 (7.1)
1 month	7.7 (6.8)	54.1 (88.2)	138.7 (67.0)	129.3 (65.8)	4.9 (1.9)	9.6 (7.5)
3 months	5.8 (6.3)	24.8 (28.4)	148.3 (68.6)	145.3 (71.2)	4.6 (1.7)	6.9 (7.0)

strength although the groups as a whole did not change significantly. Night pain was completely relieved in seven patients (four in Group A and three in Group B), and much improved in 11 (six in Group A and five in Group B). All improvements were maintained at the 6-month end of trial assessment.

On patient and physician assessments, 11 patients in Group A had a good response, of whom three became symptom-free and three had no benefit, while 13 in Group B experienced a good response and two experienced no benefit. Thus, at the end of 3 months, three patients were symptom-free, 21 were much improved and five had no benefit. These results were unchanged at the end of 6 months.

Osteoarthritis

Significant improvements were obtained in Group A in articular index, morning stiffness and functional index at the end of the first 3 months and in Group B articular index, morning stiffness, functional index and visual analogue were significantly improved by 3 months (Tables 3 & 4). Again, grip strength did not change significantly in either group. On patient and physician assessment 11 patients in Group A were improved and two were unchanged while in Group B nine were improved and four did not benefit. Seven patients (four in Group A and three in Group B) were completely free of night pain, while 11 (six in Group A and five in Group B) were considerably improved in this respect.

All patients

As can be seen from Table 4, the improvement in morning stiffness over the 3-month period was significant in all groups when assessed by the non-parametric Wilcoxon matched-pairs, signed-ranks test, but not when calculated using the 95% confidence intervals. This is not surprising given the highly skewed nature of the data for morning stiffness which does not lend itself to a parametric treatment. There were no obvious changes in the blood parameters in any group over the 6-month period.

To assess speed of response, the results after 1 month of treatment were compared in Group A and Group B using the Mann Whitney U test. Statistically significant improvements were obtained in articular index and functional index in all groups after 1 month but there were no obvious differences in either efficacy or speed of action between the stabilized mussel powder and the derived lipid extract.

Twenty-eight patients, 15 with rheumatoid arthritis and 13 with osteoarthritis, were available at the end of the study, to comment on their preferences regarding the two mussel preparations. Twelve preferred the lipid preparation considering it easier to take as the capsules were smaller and the smell was less fishy, while eight preferred the stabilized mussel powder. The remaining eight had no preference.

DISCUSSION

Since the original trial was reported in 1980,¹ laboratory assays have demonstrated anti-inflammatory

Table 3 Mean parameters (with SD) in the osteoarthritic patients at base line and after 1 and 3 months of treatment

	AI	LUT	Grip strength		VA	FI
			Right	Left		
Group A						
Base line	9.5(9.6)	52.5(63.6)	216.5(71.0)	205.0(65.2)	6.1(2.0)	10.4(4.3)
1 month	6.2(7.5)	27.8(30.7)	210.0(70.5)	205.4(65.5)	5.0(2.0)	5.8(3.9)
3 months	4.3(5.7)	24.3(31.8)	221.2(56.5)	216.5(58.2)	4.8(2.2)	4.8(3.5)
Group B						
Base line	13.7(10.9)	47.5(50.6)	189.6(86.2)	183.1(84.4)	6.1(1.4)	10.0(4.6)
1 month	8.0(7.3)	21.9(21.4)	193.1(81.9)	186.2(84.4)	5.2(1.8)	6.9(4.0)
3 months	5.5(5.7)	18.5(18.7)	206.9(82.0)	191.2(86.7)	5.0(2.0)	4.6(4.2)

Table 4 The differences between the base line and 3 months assessments for AI, LUT, VA and FI for the rheumatoid and osteoarthritic patients; 95% confidence intervals, associated p values and non-parametric Wilcoxon p values

	AI	LUT	VA	FI
Rheumatoid patients				
Group A				
Confidence interval (CI)	4.3-13.3	-35-335	-.02-3.7	2.5-10.9
p (using CI)	< 0.05	> 0.05	> 0.05	< 0.05
p (Wilcoxon)	< 0.01	< 0.05	> 0.05	< 0.01
Group B				
Confidence interval (CI)	2.8-11.5	-1.5-91.2	0.00-2.8	3.2-8.7
p (using CI)	< 0.05	> 0.05	> 0.05	< 0.05
p (Wilcoxon)	< 0.01	< 0.01	> 0.05	< 0.01
Osteoarthritic patients				
Group A				
Confidence interval (CI)	2.0-8.3	-1.2-72.8	0.1-2.6	4.1-7.9
p (using CI)	< 0.05	> 0.05	< 0.05	< 0.05
p (Wilcoxon)	< 0.01	< 0.01	> 0.05	< 0.01
Group B				
Confidence Interval (CI)	4.8-11.7	-0.4-58.4	0.02-2.1	3.8-7.0
p (using CI)	< 0.05	> 0.05	< 0.05	< 0.05
p (Wilcoxon)	< 0.01	< 0.01	> 0.05	< 0.01

activity in the powdered mussel preparations.⁶⁻¹⁰ However, assays carried out in the early 1980s in Japan and Australia revealed a considerable variation in the efficacy of some batches of mussel powder, and a stabilization process was developed and patented by Biomex Australia in the mid 1980s. This variability in efficacy may in part explain the conflicting results obtained from earlier clinical trials.²⁻⁵ The mussel powder used in the original trial was freshly prepared for us along with the fish-based placebo. Stability may well have been a problem with the material used in some of the other studies.

The double-blind placebo-controlled trial¹ was carried out in the Victoria Infirmary, Glasgow, and the present study in the Glasgow Homoeopathic Hospital. Since the benefits obtained in both studies are of a similar order it is unlikely that the location of the trial influenced the results. It is worth noting that Rooney et al¹⁸ in a trial with 100 rheumatoid patients in the placebo arm, found that only 30% were still on placebo after 2 weeks, 5% after 4 weeks and none after 4 months. They concluded that 'there is no such thing as a sustained placebo response in rheumatoid arthritis.'

The two preparations used in the present study could be distinguished by appearance, smell and taste. However, as none of the patients had previously experienced any green-lipped mussel preparations it is unlikely that they would know which preparation they were given. The dispensing pharmacy staff likewise were unaware of which preparation was which and the code was not broken until all patients had completed the 6-month period of the trial. It is therefore implausible that any knowledge of the preparations influenced the result.

The present study supports the previous findings and provides evidence for the clinical efficacy of the lipid extract. On the other hand, no obvious difference was demonstrated between the stabilized mussel powder and the lipid extract. The numbers of patients in each group, however, were small, and it is possible that with larger numbers a small difference in efficacy between the two preparations might be detectable. A similar order of efficacy is not surprising since laboratory studies¹⁹ have shown the presence of a number of N-3 essential fatty acids (N-3 EFAs) of which eicosapentaenoic acid (EPA) and dodecahexanoic acid (DHA) are believed to be among the most important, in the stabilized mussel

powder. The residue from the extraction process whereby the lipid extract was prepared, showed little in the way of N-3 EFAs and minimal biological activity. This suggests that the activity is associated with the lipid fraction rather than with the protein moiety. The anti-inflammatory and leucotriene modulating effects of these N-3 EFAs compared favourably with such routinely used NSAIDs as ibuprofen and naproxen.¹⁰

It had been suggested that since the lipid fraction was a more concentrated preparation of the N-3 EFAs than the original starting material, it might act more quickly. Three of the rheumatoid patients in the lipid extract group did experience dramatic improvements in all parameters in the first month, which were maintained until the end of the study. However, a comparison of the stabilized mussel powder and lipid extract groups after 1 month of treatment did not show any statistical difference between the two preparations. Over the entire 6-month period of the trial, using non-parametric tests, no statistical differences were observed in any parameter in either condition between the stabilized mussel powder and its lipid extract.

What was surprising was the speed with which clinical improvements were obtained, most noticeably in the articular index of joint tenderness. Comparable improvements were not obtained until after 2–3 months of treatment in the original study. It is also noteworthy that 50% of the rheumatoid patients in this study were on second line drugs whereas these had been an exclusion criterion in the original study. Taken together, these findings indicate a more powerful anti-inflammatory effect of both the stabilized mussel powder and its lipid extract than was observed with the material studied in the late 1970s.

Fresh, freeze-dried preparations of the New Zealand green-lipped mussel stabilized by Biomex's patented process appear to be beneficial to about three quarters of patients suffering from both rheumatoid arthritis and osteoarthritis. The N-3 EFA content of these preparations, which has known beneficial effects on prostaglandin and leucotriene modulation, is a possible explanation for these therapeutic effects. Both the stabilized mussel powder and its lipid extract appear, on the number of patients assessed here, to be equally efficacious and there was little difference in patient preference. Both were equally free from side-effects and both were evaluated by the majority of the patients as enhancing their quality of life. Since some patients felt better on the mussel powder and others felt better on the lipid extract, patient preference should be a relevant consideration.

ACKNOWLEDGEMENTS

The authors wish to thank Biomex, Surrey Hills, Victoria, Australia for supplying both the stabilized mussel powder and the lipid extract; the pharmacy

staff of the Glasgow Homoeopathic Hospital for carrying out the random assignments and keeping the code; and Dr Harper Gilmour of the statistical department of Glasgow University for statistical advice.

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