CURRENT THERAPEUTICS

Double blind, placebo controlled study of the mussel *Perna canaliculus* (New Zealand Green-lipped mussel) in gonarthritis (arthritis of the knee)

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INTRODUCTION

Seatone is a lyophilized extract of New Zealand green-lipped mussels (*Perna canaliculus*). This product, extracted from the mussel gonads, has been scientifically investigated for more than ten years and has been shown to have anti-inflammatory properties both in animal experimentation (1, 2, 3, 4) and in random (clinical) trials on rheumatoid arthritis (5, 6) and arthritis (6).

The aim of this study was to evaluate the efficacy of long term treatment with Seatone against placebo in arthritis of the knee. The choice of gonarthritis as a model of chronic degenerative arthropathy is justified by the frequency of this arthritic site and the chronic nature and relative stability of the pain and joint constraint, at least in its femorotibial manifestation.

MATERIALS AND METHODS

Selection of Patients

The trial was conducted on 53 patients suffering from radiological confirmed gonarthritis and showing clinical symptomatology of pain stable for several weeks. Disabling gonarthroses (ARA stage 4) and/or those resulting from recent surgical intervention were excluded.

Trial Protocols

The 53 trial patients were randomly assigned on a double blind basis to two groups, one receiving six capsules of Seatone (27 subjects) and the other (26 subjects) 6 capsules of placebo. Previous treatments (analgesic, non steroidal anti-inflammatory agents physiotherapy, re-education ...) were continued without modification. The study lasted 6 months.

The criteria of efficacy and tolerance were assessed for each patient at the beginning of the trial and then monthly to the end of the study. Ten criteria of efficacy were used:

- The functional ARA stage (stage 1 : no constraint of daily activities, stage 2 : daily activities normal despite the presence of constraint and limitation of affected joints, stage 3 : reduced daily activities, stage 4 : no daily activities)
- Huskisson's visual algometric scale (7)
- the duration of morning "limbering up time" in minutes
- the intensity of pain (1: no pain, 2: slight pain, 3: moderate pain, 4: intense pain)
- the amplitude of joint mobility
- the heel to buttock distance
- use or non-use of walking stick
- maximum walking distance
- the opinion of the patient on the course of his pain by comparison with the initial state (much better, better, a little better, the same, slightly worse, worse, much worse)
- evaluation by the clinician of the total effectiveness of the treatment (excellent, good, average, slight, none).

With regard to tolerance the following were assessed:

- the existence of related adverse effects
- an eventual protective effect of Seatone on the tolerance of the digestive trace mucosa for non-steroidal anti-inflammatory agents (8).

Statistical Analysis of the Results

The comparison between Seatone and Placebo was made for each item by calculation of averages and analysis of variance with respect to one factor for the first consultation and with respect to two factors (treatment and time) at succeeding consultations.

RESULTS

Comparability of Seatone and Placebo Groups

Analysis of the two groups showed no significant difference with respect to averages or distribution (**Table 1**), except for the shorter duration of morning mobilization for the placebo group.

Comparison of Seatone with Placebo

1. **Efficacy** - Of the ten criteria relating to effectiveness, four showed a significant difference of the averages in favour of Seatone:

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- pain assessed to Huskisson's visual algometric scale ($p<0.01$), (fig. 1)
- the functional stage (ARA) ($p<0.01$), (fig. 2)
- the opinion of the patient on the result of treatment ($p<0.05$), (fig. 3)
- the effectiveness of treatment as judged by the clinician ($p<0.01$), (fig. 4).

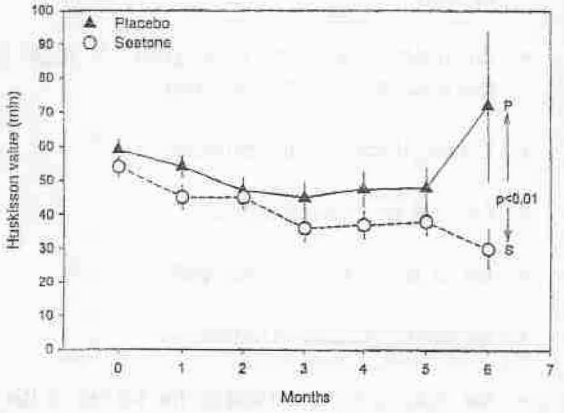

Figure 1. Timecourse of pain (evaluated by Huskisson visual method)

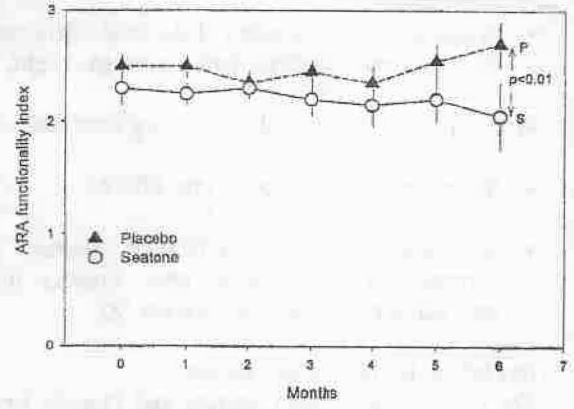

Figure 2. Timecourse of ARA function

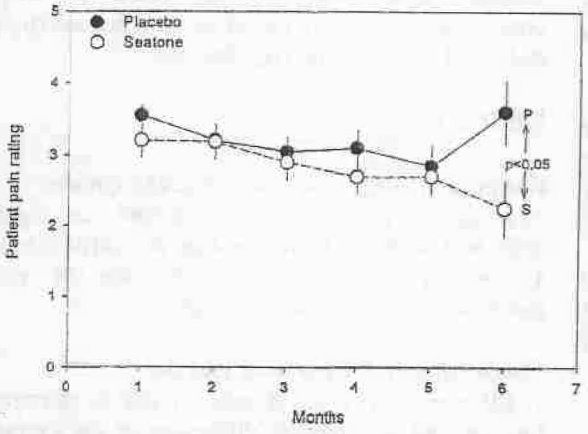

Figure 3. Timecourse of patient pain (1 = good, 5 = bad)

The duration of morning mobilization is significantly shorter with placebo ($p<0.01$) but this duration is initially lower (table 1).

Table 1	PLACEBO	SEATONE
number in group	26	27
physical parameters at entry		
male	8	8
female	18	19
age	66±11 years	65±10 years
disease severity:		
mild	3	3
moderate	16	17
severe	7	5
duration of disease	63±58 mnths	70±70 mnths
gonarthritis:		
unilateral	12	9
bilateral	14	17
radiological stage: 1	6	3
2	9	13
3	11	10
type: femur-patella	5	3
femur-tibia	4	6
general	16	17
arthritis evaluation parameters at entry		
pain intensity	3.00±0.63	2.96±0.65
Huskisson score	59+16	54±19
functional stage- ARA	2.46±0.51	2.33±0.68
morning stiffness- min	11±11	17±21
max walking distance	3.62±0.64	3.44±0.75
walking without stick	0.23±0.43	0.22±0.42
knee joint mobility	2.35±0.69	2.44±0.58
dist. heel-buttock	1.78±0.97	1.89±0.80

There is no significant difference between placebo and Seatone in the amplitude of joint mobility, the distance from heel to buttock and the intensity of pain on the analogy scale even though the curve favours the superior effectiveness of Seatone (fig. 5).

2. **Tolerance** - There was no difference in tolerance of the two products, both being well tolerated. No protective effect on gastric mucosal tolerance of non-steroidal anti-inflammatory agents was found.

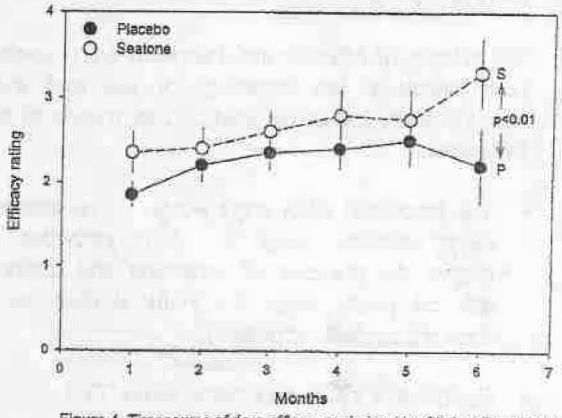

Figure 4. Timecourse of drug efficacy as judged by Clinical Practitioner (1 = no effect, 4 = strong effect)

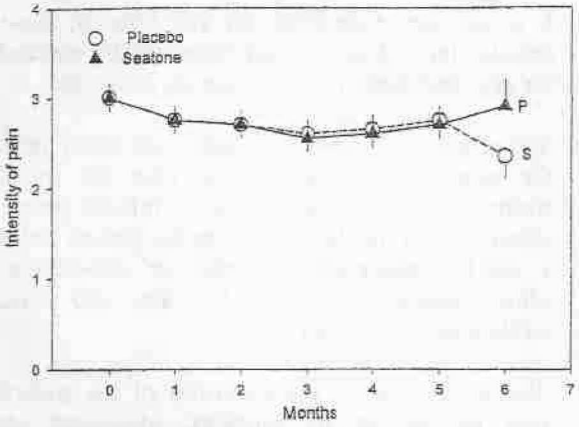

Figure 5. Timecourse of pain intensity by an analogy scale (1 = less, 4 = more intense)

3. **Influence of Original Characteristics on Results** - We tried to determine whether certain original characteristics pertaining to the patient (age, sex) or to the disease (clinical or radiological severity, anatomical location) could influence the final result for the four criteria showing a significant difference:

- sex did not affect results;
- age had no influence except insofar as it affected the "ARA" stage with Seatone showing a superior result for patients older than 65 (fig. 6);
- the severity of the disease greatly influenced the result, the Seatone treatment being effective in moderate expressions of the disease, but not in the severe forms, whatever the criterion considered:
  - Huskisson scale ($p<0.05$, fig. 7),
  - functional "ARA" stage ($p<0.01$, fig. 8),
  - patient opinion ($p<0.01$, fig. 9),
  - effectiveness judged by the clinician ($p<0.01$, fig. 10).

The significant effectiveness of Seatone can be related to radiological stages 1 and 2 and not to stage 3 (fig. 11).

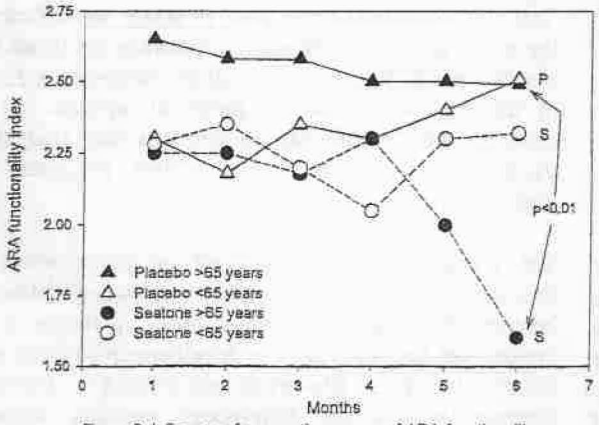

Figure 6. Influence of age on timecourse of ARA functionality

4. **Influence of Duration of Treatment on Results** - It was assessed on the clinician's evaluation of total effectiveness, this criterion being the most representative of all results.

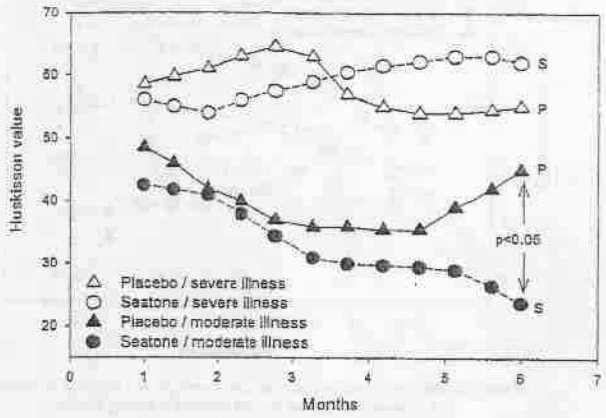

Figure 7. Effect of illness severity on timecourse of pain intensity

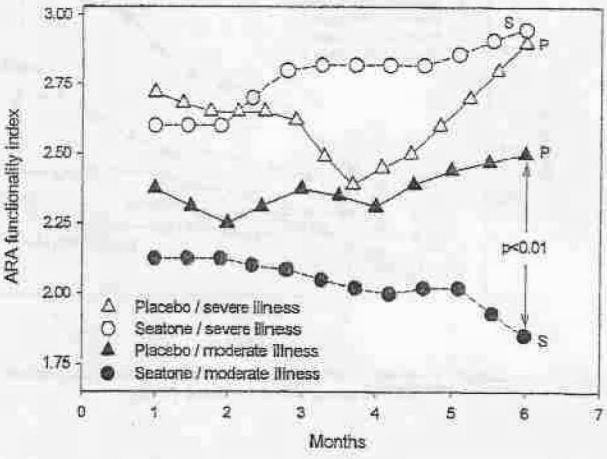

Figure 8. Influence of illness severity on timecourse of ARA function

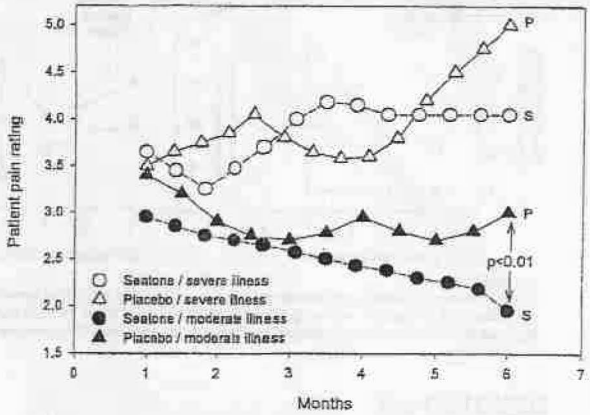

Figure 9. Effect of illness severity on timecourse of patient pain (self-assessed, 1 = good; 5 = bad)

The results for Seatone are significantly better than placebo at the 7th consultation after 6 months of treatment ($p<0.05$) and for mild or moderate gonarthrosis (fig. 12). This difference is due to extreme results, that is for patients for whom effectiveness was judged as excellent or negative. In the Seatone treated group effectiveness is judged as excellent in 40% of cases and is never negative whereas in the placebo group effectiveness is never excellent and is negative in 40% of the cases.

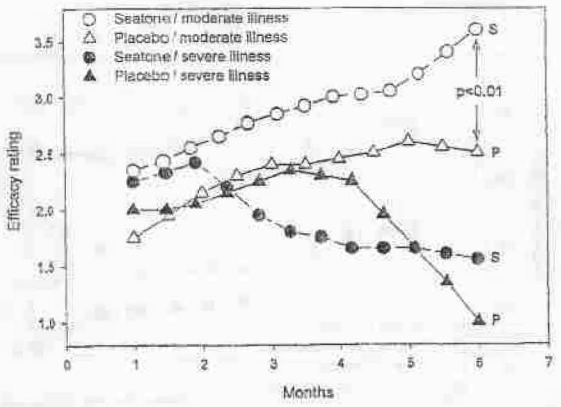

Figure 10. Effect of illness severity on timecourse of drug efficacy, as judged by Clinical Practitioner (1 = no effect; 4 = strong effect)

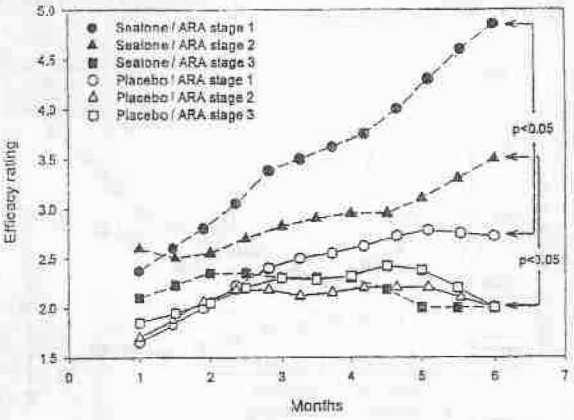

Figure 11. Effect of radiological stage on timecourse of drug efficacy (1 = no strong effect; 4 = strong effect)

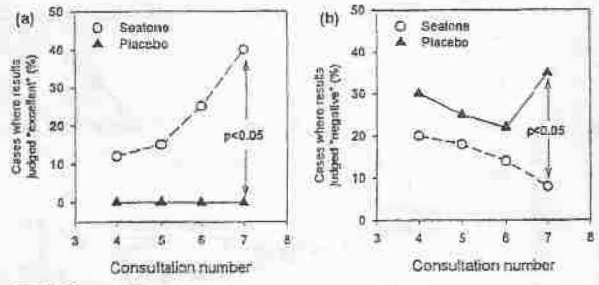

Figure 12.
Effect of treatment duration on overall result in cases of mild to moderate gonarthritis
(a) In cases where results were judged as "excellent" by the Clinical Practitioner
(b) In cases where results were judged as "negative" by the Clinical Practitioner

DISCUSSION

The results of this trial support the effectiveness of Seatone in arthritis of the knee because the curves representing the development of the averages of seven out of the ten assessment criteria favor this product and because the difference between Seatone and placebo attains the threshold of statistical significance for four of these criteria:

1. pain assessed according to Huskisson's scale,
2. "ARA" functional stage,
3. opinion of the patient on the result of treatment
4. effectiveness as judged by the clinician.

It is appropriate to point out that three of these four criteria (1st, 3rd and 4th) are those usually credited with the greatest discriminatory power by Eular (9).

The efficacy of Seatone becomes particularly evident at the term of the trial, that is after six months of treatment, which suggests that it reflects possibly an effect on the evolution of the arthritic disease rather than a purely symptomatic analgesic or anti-inflammatory effect (generally evident in less than two weeks and stable after the 15th day).

Among the original characteristics of the gonarthroses only the severity of functional (disability) and the radiological stage influence the effectiveness of Seatone which is evident mainly in the case of functionally mild gonarthroses (i.e. radiological stages 1 and 2).

This statement is compatible with the hypothesis that Seatone behaves as a "fundamental treatment" of arthritis which has no effect beyond a certain stage of development of the degenerative arthopathy at least for the dose levels used in this trial. It could also reflect a purely symptomatic analgesic or anti-inflammatory activity of low density. In any case, these data urge, in the event of further trials, the introduction of a posology (dosage regimen) appropriate to severity.

In conclusion, a controlled double blind trial was carried out to evaluate the effectiveness and clinical tolerance of an extract of the mussel, Perna canaliculus (Seatone) against placebo in arthritis of the knee.

It was conducted in 53 patients, randomly assigned to two comparable groups of respectively 26 patients receiving placebo and 27 patients treated with Seatone for 6 months, all examined initially and then monthly during the trial.

Ten clinical criteria were used to assess the efficacy of the tested product. Comparisons between the treated and placebo group for the consultations following initiation of the trial were done by statistical analysis of each criterion with calculation of averages and analysis of variance with respect to two factors (treatment and time).

The results of the trial indicate an effectiveness for Seatone expressed by a significant statistical difference between the placebo and treated group in favour of this product for four criteria; the development of three other criteria during the trial stand out equally in favour of Seatone, without the differences reaching statistical significance. Among the original characteristics of the gonarthroses only the severity of functional disability and the radiological stage influence the effectiveness of the tested product which is mainly evident in moderate cases and maximally different at the end of the trial.

Tolerance for Seatone and placebo was excellent.

The results of this preliminary trial support the effective action of Seatone in subjects suffering from mild arthritis of the knee. They prompt further study of this product on these types of patients to confirm its effectiveness and to determine optimal posology and its mode of action.

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