REVIEW
Submitted: 20 March 2010 • Accepted: 26 March 2010

Efficacy of lipid extract from *Perna canaliculus* in treatment of musculoskeletal diseases in old age

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Summary

Osteorthritis (OA) is a social disease with a multifactorial etiology. It is the most common rheumatic disease characterised by pain and inflammation due to an involvement of articular cartilage, bone and soft tissues. OA prevalence increases with age and depends on risk factors presence.

We can distinguish primary osteoarthritis chan ges, with unknown reason, greater incidence and secondary chan ges as a result of injury, metabolic factors influence Or congenital malformations.

Rheumatoid arthritis (RA) is a systemic, inflammatory and autoimmunologic connective tissue disorder of the unknown origin. Inefficaciously treated Has a chronic progressive charakter, leading to the inefficiency, the cripplehood and even the untimely death. For purposes of the therapy is the therefore quick and permanent limitation of the inflammatory process. The development of the immunology let on the enrichment of the previous therapy. They worked with the inclusion to the therapy of the enough numerous and dynamically increasing group of biological disease modifying antirheumatic drugs, especially Lyprinol. *Geriatria 2010; 4: 39-46.*

Keywords: osteoarthritis, pain, joint, biological drugs, Lyprinol

People older than 65 years constitute currently over 20% of populations of developed countries and this proportion is growing exponentially. Patient's age should not affect the standards of treatment, but treatment of older people is associated with many problems. The first is the co-morbidity of many diseases [1].

Another problem for the patients in this age group is pain. The incidence of chronic pain increases with age and in the range of 65-74 years it reaches 51% and in patients above 85 years - 55%. In addition to identification of appropriate analgesic therapy, it is very important to make an initial distinction, whether we deal with the pain associated with osteoarthritis, psychosomatic diseases, or concomitant inflammatory or neoplastic changes.

Osteoarthritis (OA) is characterized by progressive destruction of articular cartilage, as well as damage and reconstruction of subchondral layer of bones. Characteristic radiological changes of AO are found in 30% of people aged 45-64 years, while over 65 years of age - as many as 68% of people.

The pathogenesis of OA is complex. An important role in OA play factors associated with overload (microtrauma), wear and aging of tissues (apoptosis), and inflammatory mechanisms.

Osteoporosis is a systemic skeletal disease characterized by a decrease in mechanical resistance of bones and a growing risk of bone fractures. Fractures, especially of the proximal femur, are associated with increased morbidity and mortality. Bone resistance is determined by the bone mineral density (BMD*)* , which can be measured by densitometry, and the quality of bone tissue, which so far is not subject to reliable measurement [1].

In patients over 60 years of age also the acute onset of rheumatoid arthritis is frequently observed (fever, involvement of many joints, high rates of inflammation, weight loss, rapid progression). The disease can start with involvement of large joints; initially, the patients often meet the diagnostic criteria for PM (polymyositis).

In older people, occurs sometimes the RA "overdiagnosis" because of frequent incidence of degenerative hand disease, as well as rheumatoid conditions (in 10-25% of healthy people over 70 years of age).
Rheumatoid arthritis starting in the old age *(Elderly Onset Rheumatoid Arthritis* - EORA), ie over 60 years, is different in clinical presentation and course from rheumatoid arthritis beginning in the younger age *(Younger Onset Rheumatoid Arthritis* - YORA) in the following characteristics: comparable morbidity of both sexes, acute onset, frequent involvement of large joints (especially shoulder) and higher disease activity. Long-term observational studies have shown a greater progression of radiographic changes in joints and greater impairment of functional capacity in patients with EORA than in patients with YORA. These differences relate mainly to seropositive patients. In sero-negative patients the course of disease is usually milder, showing features of polymyalgia rheumatica or symmetrical synovitis of hands with accompanying severe swelling. This

report is a review of the literature on differences in clinical course and presentation of EORA compared with YORA [2].

Another problem is osteoarthritis (OA), currently the most common and one of the most troublesome medical problems of people in middle and old age. It is the most common cause of reduced efficiency of majority of the population and an increasingly frequent cause of professional inactivity. 60% of patients over 35 years of age complain of pain in various joints, suggesting that the degenerative changes are not only the effect of tissue aging, but also the result of much more complex processes. According to the definition proposed in 1995 by Goldberg and Keuttner, the onset of the disease is influenced by both biological and mechanical phenomena. Their joint action leads to an imbalance between joint cartilage synthesis and degradation process. This justifies calling them a disease [3].

In pharmacotherapy of OA, paracetamol is considered the safest first-line drug. In case of patients whose response to paracetamol is insufficient, the treatment with non-steroid anti-inflammatory drugs (NSAIDs) alone or in combination with paracetamol is applied. The frequency of administration and dosage should depend on the severity of pain perceived by the patient. There is no need for constant, chronic administration of NSAIDs. NSAIDs which are being applied can be substituted by a different drug from the same group, if they do not give the expected therapeutic effect. When a long-term therapy is expected, only safe drugs should be recommended, such as preferential COX-2 inhibitors (Nabumetone, Nimesulide, Meloxicam) or selective COX-2 inhibitors (Celecoxib). This reduces significantly the risk of side effects in gastrointestinal tract. However, it turned out that selective COX-2 inhibitors may increase the risk of thromboembolial complications [4].

Therefore, there is a growing tendency among the patients to seek alternative drugs against rheumatic diseases. This is probably due to reports of the toxicity of prescription nonsteroidal anti-inflammatory drugs (NSAIDs). There are doubts, whether the most popular alternative therapies bring relief, or lead to side effects.

Among the 37 herbal preparations tested, seven were equally effective as ibuprofen in the anti-arthretic test, without causing gastrointestinal bleeding. Five of the ten tested products of animal origin was also effective, with no apparent toxicity. Within certain classes of products, such as substances from celery seed or dried preparations of mussels, the efficiency ranged from zero to very high [5].

Whitehouse et al demonstrated that products obtained from celery "seed" showed either effective anti-inflammatory action, or almost no action (the latter situation seems to dominate). Two specific types of products from marine organisms, from the New Zealand mussel or Australian edible holothurian (so-called "sea cucumber"), similarly showed potency ranging from high efficiency, to absence of measurable anti-inflammatory activity, respectively.

Many products, widely advertised as effective in treating arthritis (eg fish oils, ginger extracts, glucosamine sulfate) had no effect on the development of polyarthritis in rats, even after extended dosing (up to 16 days). Commercial sample of cetyl-M *(cetyl meristoleate)* to which anti-arthretic action in rats was attributed (Diehl and May, 1994), also did not show any activity [6].

In scientific world, a lipid preparation from the New Zealand green-lipped mussel *Perna canaliculus* aroused huge interest.

Laboratories are interested in the two versions of the drug, which source is the mussel: dry powder and lipid extract.

About 20 years ago, appeared the awareness of therapeutic potency of lyophilized green-lipped mussel *Perna canaliculus.* An open, 4-year study conducted on the patients of Homoeopathic Hospital in Glasgow, UK, who have not responded to first-line drugs, have shown that it is beneficial both in rheumatoid arthritis, and osteoarthritis [7]. Double-blind clinical trials have shown that it has brought relief to 68% of patients with RA and 40% suffering from osteoarthritis. Improvement was evident in the severity of pain, degree of morning stiffness, mobility, and night-time pain.

S.L.M. Gibson and R.G. Gibson from Glasgow Homoeopathic Hospital in Glasgow, UK analyzed for a long time the effectiveness of lipid extract from the New Zealand green-lipped mussel (Lyprinol) in rheumatic diseases and compared it with the raw powder from that same mussel.

Sixty new patients visiting the clinic of Homeopathic Hospital in Glasgow were invited to participate in clinical trials, of whom 30 had classical rheumatoid arthritis, and 30 had clinical and radiological signs of osteoarthritis. Calculations based on the results of double-blind study showed that 7-10 patients per group are enough to demonstrate 50% reduction in symptoms, with 95% probability. Fifteen patients per group was therefore considered a sufficient number.

Improvement in morning stiffness after 3 months was significant in all groups, as calculated by nonparametric paired Wilcoxon signed rank test, however it was not significant when using 95% confidence interval. This is not surprising, considering the small amount of highly scattered data. Blood analysis results did not change significantly in any of the groups during the study. To assess the rate of reaction to the preparation, the results obtained after one month were compared between the A and B groups using the Mann-Whitney U-test. A statistically significant improvement was observed in the articular index and functional index in both groups after 1 month, but there was no clear difference between the rates of action of powder and stabilized lipid extract [7,8].

In 2000 Michael Whitehouse from the University of Queensland, Australia compared Celebrex and Vioxx - two COX-2 inhibitors - with Lyprinol and Anaproxen (NSAID, naproxen has been used clinically since 1972) in laboratory rats. In doses 15 mg / kg of body weight, Celebrex and Lyprinol provided protection against artificially induced arthretic inflammation in rats to almost the same extent (78% reduction in inflammation). Vioxx did not reduce the

inflammation, if the dose was not significantly increased. Then it reduced the inflammation only minimally. Anaprox achieved good results reducing inflammation by over 80%. However, it caused the largest number of adverse actions in the gastrointestinal tract. The rest of the agents did not cause any adverse effects in the gastrointestinal tract. Whitehouse found that Lyprinol was as effective as Celebrex and showed no adverse effects [9].

Whitehouse also compared the efficacy of Lyprinol to the effectiveness of a prescription drug - Indomethacin. He demonstrated that at the dose of 5 mg / kg of body weight, Lyprinol showed 97% efficacy in reducing swelling. In contrast, Indomethacin which at this dose is toxic, reached only 83% efficacy [10].

Chak Sing Lau from the Queen Mary University Hospital in Hong Kong, organized a double-blind study conducted in this hospital. He compared the action of Lyprinol with placebo with regard to signs and symptoms and quality of life of patients with osteoarthritis of the knee. Eighty patients with osteoarthritis of the knee were randomly assigned to one of the groups receiving either Lyprinol, or placebo for 6 months [11].

Improvements in almost all arthritis assessment parameters was observed in both groups, which confirmed the need for placebo-controlled studies. The placebo effect can be significant and lead to false, optimistic conclusions. However, there was a significantly higher degree of improvement in pain (VAS) and overall patient's assessment of arthritis, in subjects who took lipid extract from mussels, compared to those who took placebo. This significant difference remained even after adjusting the results by number of paracetamol/acetaminophen (Tylenol) taken to control pain. It was observed in the fourth week, which confirms the slow action of the lipid extract. Patients who took Lyprinol also scored higher in two physical and psychological parts of CAIMS2-SF in forth week, which means better quality of life. Lipid extract from mussels was safe and well tolerated by all patients [11].

A Group of physicians in Germany investigated the efficacy and safety of combination of green lipped mussel extract with high concentrations of fish oils containing EPA and DHA in patients with rheumatoid arthritis (AR). This 12-week study was conducted on 50 adult individuals, men and women. Total number of 34 patients required pharmacological treatment before and during the study. At the end of the study, 21 (62%) of them were able to reduce their dose, and most importantly, 13 of them were able to discontinue all medications. At week 12, 38% had no symptoms, and the number of patients complaining of severe pain decreased significantly from 60% (at baseline) to 25% at the end. A special combination of green lipped mussel lipid extract and selected omega-3 fatty acids was very well tolerated, with a single case of transient mild nausea [12].

Theo Maccrides was leading a research team from the Royal University Institute of Technology in Melbourne from 2005 to 2008 and published the work in succesive editions of *Comparative Biochemistry and Physiology.* Part B regarded both Lyprinol, available on the market, and mussel extracts obtained by extraction in supercritical carbon dioxide ($C0_2$) and their impact on COX (cycloxygenase) and leukotriens levels *in vitro.* The researchers reported that the commercial extract - Lyprinol showed a strong ability to inhibit COX-1 and COX-2. Free fatty acids and triglyceride fractions were identified as active, anti-inflammatory components. According to research reports, extract hydrolysis with potassium hydroxide or proteases increased COX inhibition 10-fold. The authors formulated the following conclusion: "These results confirm the usefulness of the commercial mussel extract, Lyprinol, as an alternative to conventional non-steroidal anti-inflammatory drugs (NSAIDs) and fish oil therapy in reducing the symptoms of arthritis [13].

In conclusion, the action of Lyprinol results from the synergy of 4 or 5 different polyunsaturated fatty acids. Together with currently known fatty acids: EPA (eicosapentaenoic), DPA (docosapentaenoic) and DHA (docosahexaenoic), 2 or 3 fatty acids of unknown chemical structure play a role in the anti-inflammatory action of Lyprinol [14]. It is known that the mechanism of anti-inflammatory action of Lyprinol is the inhibition of lipoxygenase pathway, responsible for the conversion of arachidonic acid to leukotrienes in the cell membrane. In this way, Lyprinol prevents the migration of neutrophils and improves symptoms associated with degenerative diseases, such as pain, swelling, stiffness, fever, which in turn improves the quality of life of elderly patients.

The application of Lyprinol should therefore be taken into consideration in treatment of inflammation of joints as an addition to the methods of treatment being applied, which may result in a reduction of pain and swelling and allow reduction of doses of first-line medicines [15].

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