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RESEARCH ARTICLE

Abexol: a therapeutic option for the management of symptoms in patients with osteoarthritis

Abexol: una opción terapéutica para el manejo de los síntomas en pacientes con osteoartritis

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ABSTRACT

Osteoarthritis is a degenerative joint disease that affects hundreds of millions worldwide, mainly the elderly. The management of osteoarthritis included a combination of non-pharmacological interventions and pharmacologic agents. Abexol, a mixture of beeswax alcohols with antioxidant, gastroprotective and anti-inflammatories effects demonstrated in experimental and clinical studies. The objectives of this work are framed in addressing the results of six randomized clinical studies conducted with Abexol on symptoms in patients with osteoarthritis: two to double blind, placebo controlled six and eight weeks of treatment, one comparative with Lyprinol, another comparative with Prevenox and its combined therapy, and two open, comparative with Chondroitin sulfate/Glucosamine three and six month of treatments. The primary outcome was the reduction of the total WOMAC score. Secondary outcomes included WOMAC pain, stiffness and function scores and VAS score. The reduction of consumption of analgesics was a collateral outcome. In all studies the data were analysed as per the Intention to treat approach. Abexol treatment produced a documented clinical improvement in patients with osteoarthritis, which was reflected in a significant improvement in pain, stiffness, physical activity and overall symptomatic status, through the total WOMAC score and score of pain of the VAS scale, with an efficacy superior to Lyprinol and comparable to Prevenox and Chondroitin sulfate/Glucosamine. Abexol treatment significantly reduced the consumption of analgesics in these patients. The treatments were safe and well tolerated. It is concluded that according to the efficacy and safety shown by Abexol in the treatment of patients with osteoarthritis, Abexol could be an alternative for the management of these patients, mainly in those patients who have contraindicated treatment with non-steroidal anti-inflammatories and paracetamol.

Keywords: Abexol; beeswax alcohols; osteoarthritis; WOMAC score; VAS score.

RESUMEN

La osteoartritis es una enfermedad articular degenerativa que afecta a millones de personas en todo el mundo, principalmente a los ancianos. El manejo de la osteoartritis incluyó una combinación de intervenciones no farmacológicas y agentes farmacológicos. El Abexol es una mezcla de alcoholes de cera de abejas con efectos antioxidantes, gastroprotectores y antiinflamatorios demostrados en estudios experimentales y clínicos. Los objetivos de este trabajo se enmarcan en abordar los resultados de los seis ensayos clínicos aleatorizados desarrollados con el Abexol sobre los síntomas en pacientes con osteoartritis: dos a doble ciegas, controlados con placebo de seis y ocho semanas de tratamiento, uno comparativo con Lyprinol, otro comparativo con Prevenox y su terapia combinada, y dos abiertos, comparativos con Condroitín sulfato/Glucosamina de tres y seis meses de tratamiento. La variable primaria de eficacia fue la reducción del puntaje total de la escala WOMAC. Como variables secundarias de eficacia se prefijaron la reducción de los puntajes de los dominios dolor, rigidez y actividad física de la escala WOMAC y del puntaje de la escala VAS y como variable colateral de eficacia se evaluó la reducción del consumo de analgésicos. En todos los estudios, los datos se analizaron según el método de Intención de tratar. El tratamiento con Abexol produjo una mejoría clínica documentada en pacientes con osteoartritis, que se reflejó en una mejora significativa en el dolor, la rigidez, la actividad física y el estado sintomático general, a través del puntaje total de la escala WOMAC y el puntaje de dolor de la escala VAS, con una eficacia superior a Lyprinol y comparable a Prevenox y Condroitín sulfato/Glucosamina. El tratamiento con Abexol redujo significativamente el consumo de analgésicos en estos pacientes. Los tratamientos fueron seguros y bien tolerados. Se concluye que de acuerdo a la eficacia y seguridad mostrada por el Abexol en el tratamiento de pacientes con osteoartritis, el Abexol podría constituir una alternativa para el manejo de estos pacientes, principalmente en aquellos pacientes que tienen contraindicado el tratamiento con anti-inflamatorios no esteroidales y paracetamol.

Palabras claves: Abexol; alcoholes de cera de abejas; osteoartritis; puntaje WOMAC; puntaje VAS.

INTRODUCTION

Osteoarthritis is the most common joint disorder characterized by pain associated with stiff joints and is a leading cause of disability in the elderly (Briggs *et al*, 2016).

The optimal treatment for the management of osteoarthritis uses the combination of non-pharmacological and pharmacological treatment. Non-pharmacological treatment is based on adopting lifestyles that include reducing overweight, practicing moderate but systematic physical activity, specific exercises in the affected region, correcting postures, together with physical and rehabilitation medicine. In addition, various orthotics are also used (splints, canes, crutches, corsets, among others). However, very often these measures are insufficient and pharmacological therapy is essential (Hochberg *et al*, 2012; McCarberg & Tenzer, 2013).

Current guidelines recommend the use of non-steroidal anti-inflammatories (NSAIDs) to improve symptoms despite not solving the cause of the pathological process. NSAIDs are medications that inhibit the enzyme cyclooxygenase (COX) and are widely used as antiarthritic medications, specifically to treat inflammation and pain that accompany osteoarthritis. NSAIDs produce various adverse events: nonspecific NSAIDs that inhibit both COX-1 and COX-2 (aspirin, diclofenac, ibuprofen, naproxen, indomethacin, piroxicam, among others) primarily cause gastrointestinal disorders, while specific or inhibitors of COX-2 are associated with an increase in cardiovascular risk (Cutolo *et al*, 2015; Yeomans, 2015).

Other therapeutic classes used in the pharmacological treatment of osteoarthritis are corticosteroids and analgesics (acetaminophen, tramadol, codeine), and less frequently, opioid analgesics (Allen *et al*, 2015).

However, due to the gastrointestinal adverse effects produced by non-selective and cardiovascular NSAIDs, by specific COX-2 inhibitors and acetaminophen-associated hepatoxicity, the search for new, safer and better tolerated alternatives is justified (Lee *et al*, 2010).

It has been shown that some compounds can produce beneficial effects on articular cartilage, such as slow-acting drugs or SYSADOA (acronym for Symptomatic Slow Acting Drugs for Osteoarthritis) that have overall efficacy similar to NSAIDs, but their effect takes longer to be achieved and persists for a few months after treatment suppression. This group includes drugs such as hyaluronic acid that is administered intraarticularly, chondroitin sulfate and glucosamine sulfate administered orally. All of them are part of the cartilage matrix, and have advantages over NSAIDs because they have greater security (Henrotin & Lambert, 2013).

Clinical trials conducted with chondroitin sulfate, glucosamine sulfate and hyaluronic acid have shown the possibility that these compounds, in addition to acting as drugs of slow symptomatic action, can influence the course of osteoarthritis (slowing or delaying the disease), is that is, they act as modifiers of the course of arthrosis disease (Singh *et al*, 2015).

Other products of complementary or traditional medicine with antioxidant and/or anti-inflammatory properties, have shown encouraging results, such as Lyprinol, a lipid extract composed of a mixture of fatty acids and carotenoids obtained from mussel New Zealand green lip, registered as a nutritional supplement, which in clinical studies has shown to be effective in reducing pain, inflammation and stiffness in subjects with osteoarthritis, as well as improved functionality in the affected joints (Kim, 2014).

On the other hand, Prevenox (D-003), a mixture of high molecular weight aliphatic acids from sugar cane wax[11] registered as a nutritional supplement, with antioxidant and anti-resortive effects demonstrated in experimental and clinical studies (Pérez *et al*, 2008; Mendoza *et al*, 2005; Ceballos *et al*, 2011), it has also been effective in subjects with osteoarthritis (Puente *et al*, 2014a).

Abexol (D-002) is a mixture of six higher primary aliphatic alcohols obtained from beeswax (*Apis mellifera*) (Mas, 2001), registered as a nutritional supplement, which inhibits the activity of cyclooxygenase and 5 lipoxygenase enzymes (Pérez *et al*, 2014), with antioxidant, gastroprotective and anti-inflammatories demonstrated in experimental and clinical studies (Menéndez *et al*, 2000; 2001a; 2001b; Molina *et al*, 2001; Pérez *et al*, 2002; Mendoza et al, 2007; López *et al*, 2008; Rodríguez *et al*, 2009a).

Abexol has been effective in models of acute inflammation (edema of the leg induced by dextran, histamine and serotonin in rats, edema induced by xylene in the mouse ear) and in models of chronic inflammation such as granuloma induced by cotton speck (Carbajal *et al*, 1998; Ravelo *et al*, 2010a; 2010b).

Unlike the gastrotoxicity that accompanies NSAIDs, Abexol does not produce gastroduodenal damage, made compatible with its dual anti-inflammatory action and its gastroprotective effects demonstrated in experimental and clinical studies (Illnait *el al*, 2005; Rodríguez *et al*, 2009b; Hano *et al*, 2001, Fernández *et al*, 2012; Fernández *et al*, 2008). This action is related to a multifactorial mechanism that involves on the one hand the improvement of quality (increased glycoprotein concentration) as well as increased gastric mucus secretion; antioxidant effects that involve the reduction of hydroxyl radical generation, lipid peroxidation, protein oxidation and indicators of the degree of inflammation, such as the myeloperoxidase enzyme, as well as an increase in the activity of antioxidant enzymes in the gastric mucosa (Carbajal *et al*, 1995; 1996; 2000).

Correspondingly, clinical studies have shown that Abexol significantly improves gastrointestinal symptoms in patients undergoing NSAIDs therapy, in middle-aged and elderly subjects, and even in patients with duodenal ulcer, in which it helped improve the frequency of healing of the ulcers. In addition, an open study showed that treatment with Abexol improved the perception of health and habitual symptoms such as heartburn, asthenia and osteomyoarticular symptoms in subjects of middle and advanced age who consumed it routinely, and was very well tolerated in the conditions of clinical practice routine (Illnait *el al*, 2005; Rodríguez *et al*, 2009b; Hano *et al*, 2001, Fernández *et al*, 2012; Fernández *et al*, 2008).

In experimental studies, Abexol was effective in osteoarthritis models, both in the one induced by formaldehyde and by sodium monoiodoacetate, where it reduced not only the degree of inflammation, but the damage of cartilage (Mendoza *et al*, 2013a; 2013b). Such results prompted the corresponding clinical trials in patients with symptoms of osteoarthritis.

MATERIALS AND METHODS

The objectives of this work are framed in addressing the results of clinical studies conducted with Abexol on symptoms in patients with osteoarthritis.

The clinical studies protocols were approved by the Institutional Ethics Committee of the Surgical and Medical Research Centre (Havana, Cuba) and registered on Cuban Public Registry of Clinical Trials. The studies were conducted according to the ethical standards of Helsinki Declaration (World Medical Association, Sudafrica 2008). At enrolment, patients provided their informed written consent after received, simple and understandable language, oral and written explanations about the purpose and details of the trial.

Six clinical trials were conducted: two randomized, double-blind, placebo-controlled six and eight weeks of treatment, one randomized, comparative with Lyprinol, another randomized comparative with Prevenox and its combined therapy, and two open, randomized, comparative with Chondroitin sulfate/Glucosamine three and six month of treatments (Rodríguez *et al*, 2012; Puente *et al*, 2014b; 2014c; 2016; 2017; 2019).

Physical examinations, treatment compliance, symptom assessment, use of rescue medications and AE were controlled at each visit post-randomization. The laboratory indicators evaluated were monitored at the beginning and at the conclusion of respective treatments.

The studies enrolled ambulatory women and men (20-80 years) previously diagnosed of suffering knee, hip or finger osteoarthritis, supported by clinical and radiological criteria. Participants should have a diagnosis of functional class I, II or III (mild to moderate) according to the American College of Rheumatology criteria (Altman *et al*, 1991) and a Western Ontario and McMaster Individual Osteoarthritis Index (WOMAC) ≥ 25 and with osteoarthritis symptoms (joint pain in the hip, spine, members and/or phalanges) (Jinks *et al*, 2002).

Each of them in the respective consultations underwent a physical examination and the WOMAC Index and the VAS (Visual Analogy Scale) pain scale were applied (Bellamy *et al*, 2011; Villanueva *et al*, 2004).

Exclusion criteria were other forms of arthritis, arthroscopy performed within the past year, intra-articular injection of steroids within the past three months, uncontrolled hypertension (diastolic pressure 120 Hg mm) or diabetes (fasting glucose > 7 mmol/L), active liver or renal disease, malignancies, any other serious illnesses,

hospitalization during the 6 months prior to the study. Pregnant women, nursing women, and those not taking adequate contraceptive measures were also excluded.

Predefined premature discontinuations included unwillingness to follow-up, any adverse events supporting such decision and protocol violations (failure of tablets intake ≥ 10 days).

Tablets of Abexol (50 mg) and Prevenox (5 mg) (MedSol Laboratories, Havana, Cuba) and Lyprinol capsules (50 mg) and Chondroitin sulfate/Glucosamine (375/300 mg) (Aspen Pharma Pty Ltd, NSW, Australia) were used in these trials. Treatments were packaged in plastic bottles.

Eligible patients were randomly allocated to receive tablets of Abexol, Prevenox, capsules Lyprinol or Chondroitin sulfate/Glucosamine. The tablets or capsules should be taken one per day with the breakfast.

The randomisation code was computer-generated with a fixed, not stratified randomisation method, using balanced blocks of 8 and allocation ratio of 1:1. The doses of Abexol, Prevenox, Lyprinol and Chondroitin sulfate/Glucosamine have been used in previous clinical studies in osteoarthritis patients (Lee *et al*, 2010; Henrotin *et al*, 2013; Kim, 2014; Puente *et al*, 2014a; Rodríguez *et al*, 2012).

Treatment compliance was controlled by counting the remainder tablets or capsules and interviewing the patients. At study ending, non-used tablets or capsules were recovered. Compliance was considered good if the participants have taken at least 85% of the tablets or capsules scheduled from the previous visit.

Consumption of NSAIDs, steroids, cartilage or calcium supplements, or any other agent that may affect the study outcomes was forbidden, except that of rescue medications needed to treat persistent pain: acetaminophen (maximum 2 g/day) or metamizole (maximum 600 mg/day). Participants filled a daily record of their consumption of rescue medications, which was reported at each next scheduled visit, when the number of consumed rescue medication was recorded.

The primary outcome in all studies was a significant reduction of the total WOMAC index ≥ 30% as compared to baseline. The WOMAC questionnaire consists of three sections, one that assess pain intensity (5 questions), other joint stiffness (2 questions), and the third the physical function (17 questions). Individual responses were scored on the following scale: 0 (none), 1 (slight), 2 (moderate), 3 (severe) and 4 (extreme). The total score ranges from 0 (the best) to 96 (the worst). This tool provides a validated assessment of the patient's functional capacity, specifically joint pain, stiffness and functional impairment, being useful for the evaluation of the effect of investigational products on osteoarthritis symptoms.

Significant decreases in pain, stiffness and physical function WOMAC scores, as well as in the Visual analogy scale (VAS) score (specific for pain) were secondary outcomes. In order to avoid biases, subjects answered to both WOMAC and VAS questionnaires in the doctor's office before their examination. The VAS-visual analogy scale score used a 100 mm linear measure of pain status with 0 representing no pain and 100 the worst suffered pain. Patients marked on the linear scale the relevant amount of pain they were suffering, and the value was noted.

The consumption of analgesics was a collateral outcome in all studies. All primary, secondary and collateral outcome measures were assessed at each visit.

Safety variables included physical (body weight, pulse rate, blood pressure) and blood indicators (alanine aminotransferase –ALT-, aspartate aminotransferase–AST-, serum fasting glucose, creatinine, cholesterol, triglycerides). Blood biochemistry indicators were assessed by using reagent kits (Roche, Switzerland) and performed in the Hitachi 709 autoanalyser (Tokyo, Japan). Analyses were done at the clinical laboratory. Controls of the precision and accuracy of the methods were performed.

An adverse event (AE) was defined as any new undesirable experience or change in physical or laboratory data or the worsening of any pre-existing condition occurred through the trial, being or not drug-related. AE were classified according to their intensity in mild, moderate and serious. Mild AE were those AE not requiring treatment or withdrawal of study medication, moderate AE required withdrawal of study medication and/or specific treatment of the AE, and serious AE (SAE) was considered any AE leading to patient hospitalisation and/or death, independently of their nature (CECMED, 2007).

In all studies the data were analysed as per the Intention to treat approach. So, data of all randomized patients were included in all analyses. The samples size estimation assumed a difference of 30 % between the reductions of WOMAC total scores from baseline with each treatment at study completion.

The changes within each group of the continuous variables as well as the comparisons between groups were analyzed by Student's t test for paired samples and for independent samples, respectively. The categorical variables were analyzed with χ^2 test. For the statistical analyzes, the statistical systems SPSS 21 on Windows 10 and the EPIDAT 3.1 were used. All the statistical tests used were two tails. A priori a level of a = 0.05 was established for statistical significance.

RESULTS AND DISCUSION

The progression of osteoarthritis affects the quality of life of the sufferers.[1-3] Pain decrease and improved function are the main objectives in osteoarthritis management, which mainly involves medical treatment and lifestyle modifications (Cutolo *et al*, 2015; Allen *et al*, 2015).

Four hundred ten patients (410) with diagnosis of osteoarthritis confirmed by radiological criteria were included in the treatment phase. In all studies the groups were well balance at baseline. The patients included (average age: 64 years) were mostly women (75.9 %), which coincides with reports of higher incidence of the disease in women and more marked in the post-menopause.

The studied population presented a high frequency of risk factors, results that agree with the reports of coexistence of osteoarthritis and hypertension, overweight, obesity, dyslipidemia, smoking and diabetes in people with middle or advanced age and that can influence the development of osteoarthritis.

Fourteen patients (3.4 %) withdrawal from the studies by different causes: protocol violation (no desire to continue) (10 patients), travels (1 patient) and moderate adverse events (3 patients).

With the exception of the fourteen patients who were discharge, the rest of the patients included consumed all the tablets or capsules programmed for each stage according to the count of remaining tablets or capsules and interrogation of the patients, which shows an excellent adherence to the treatments, similar in all groups.

In all studies the efficacy of the treatments was remarkable and comparable. Since the study groups were homogeneous at baseline, the randomized allocation of treatments should be accepted as adequate and the results here seen as attributable to the treatments, not to initial differences between them.

The treatments produced comparable reductions in the primary and secondary efficacy variables in all evaluations of the WOMAC and VAS surveys conducted during the established treatment times.

In the two short-term placebo-controlled studies of six and eight weeks of treatment, from the first week of therapy, there was a significant reduction in the values of the total score and by domain of the WOMAC scale in the Abexol group, as well as the VAS scale score, with respect to the baseline level and the placebo group, reductions that were accentuated at the end of six and eight weeks of treatment, respectively (Rodríguez *et al*, 2012; Puente *et al*, 2014b).

The proportion of patients who required to consume analgesic during these studies was significantly lower in the Abexol group (10%) compared to the placebo group (56.7%) (Rodríguez *et al*, 2012; Puente *et al*, 2014b).

Regarding the comparative study Abexol versus Lyprinol in the short term of six weeks of treatment, both groups were statistically similar in baseline conditions and from the first week of treatment produced a significant reduction in the values of each domain and the total scale score WOMAC, as well as the VAS scale score with respect to the baseline level, a reduction that was significantly higher in the Abexol group compared to the Lyprinol group at the end of the six weeks of treatment (Puente *et al*, 2014c).

The proportion of patients who required consume analgesic during this study was significantly lower in the Abexol group (12%) than in the Lyprinol group (60%) (Puente *et al*, 2014c).

On the other hand, in the study where the effects of the treatment with Abexol versus Prevenox and its combined therapy were compared, the groups were also statistically similar in baseline conditions and from the first week of treatment, in the groups treated with Abexol, Prevenox and combined therapy there was a significant reduction in the values of each domain and the total score of the WOMAC scale, as well as the score of the VAS scale, with respect to the baseline level and the placebo group, reductions that were accentuated at the end of the six weeks of treatment. In addition, the reductions achieved by the combined therapy at the end of the six weeks of treatment, were significantly greater ($p < 0.01$) than those obtained by the respective monotherapies (Puente *et al*, 2016).

The proportion of patients who required to consume analgesic during this study in the Abexol (3/30, 10%), Prevenox (2/30, 6.7%) and Abexol-Prevenox (2/30, 6.7%) groups was significantly lower ($p < 0.001$) than in the placebo group (17/30, 56.7%) (Puente *et al*, 2016).

In the study where the effects of Abexol versus Chondroitin sulfate/Glucosamine treatment were compared for three months, from the second week of therapy, in both groups there was a significant reduction in the values of each domain and the total score of the WOMAC scale, as well as the VAS scale score, with respect to the baseline level, comparable reductions that were accentuated at the end of the three months of treatment (Puente *et al,* 2017).

Finally, and taking into account the previous results, both treatments were compared for a longer period of time (six months). In this study the groups were statistically similar in the baseline conditions and after six weeks of treatment there were significant reductions in the values of the total WOMAC score, of each domain (pain, stiffness and physical activity), as well as of the VAS score, with respect to the baseline level, both in the group that received Abexol and in the Chondroitin sulfate/Glucosamine treatment, reductions that were accentuated at the end of the six months of treatment. No significant differences were found between the groups in any of the evaluations carried out during the six months of treatment. (Puente *et al*, 2019).

The proportion of patients who required use analgesic during these studies was similar and comparable in both groups: Abexol (12/30, 40%) and Chondroitin sulfate/Glucosamine (11/30, 36.7%) (Puente *et al*, 2017; 2019).

Abexol treatment produced a documented clinical improvement in patients with osteoarthritis, which was reflected in a significant improvement in pain, stiffness, physical activity and overall symptomatic status, through the total WOMAC score and score of pain of the VAS scale, with an efficacy superior to Lyprinol and comparable to Prevenox and Chondroitin sulfate/Glucosamine (Rodríguez *et al*, 2012; Puente *et al*, 2014b; 2014c; 2016; 2017; 2019).

Abexol treatment significantly reduced the consumption of analgesics (collateral efficacy variables) in these patients with osteoarthritis, and in this aspect was superior to Lyprinol and comparable to Prevenox and Chondroitin sulfate/Glucosamine (Rodríguez *et al*, 2012; Puente *et al*, 2014b; 2014c; 2016; 2017; 2019).

The mechanism by which Abexol improve symptoms in patients with osteoarthritis is not an objective of studies. However, in experimental studies it has been shown that Abexol inhibits the activity of COX-2 and LOX[17] in addition to chondroprotector effects (Mendoza *et al*, 2013).

Abexol produces gastroprotection unlike the gastrotoxicity induced by NSAIDs. The gastroprotective effects involve the increase of the secretion and improvement of the composition of the gastric mucus that acts as a defensive factor of the gastric mucosa and reduces the generation of hydroxyl radicals, lipid peroxidation and protein oxidation in the gastric mucosa (Carbajal *et al*, 1995; 1996; 2000).

Short and medium term Abexol showed a good safety and tolerability profile in patients with osteoarthritis, which is consistent with reported data for this nutritional supplement. In the analysis of the effects on the physical indicators, laboratory analysis and report of adverse events during the studies no significant changes obtained in any of the comparisons made (Rodríguez *et al*, 2012; Puente *et al*, 2014b; 2014c; 2016; 2017; 2019).

CONCLUSIONS

These data demonstrate the efficacy and safety of Abexol in the management of patients with osteoarthritis, which suggests that Abexol could be an alternative, mainly in those patients who have contraindications for the treatment with NSAIDs and paracetamol.

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