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Effects of Abexol (D-002): A Mixture of Beeswax Alcohols, on Joint Discomforting Symptoms in Healthy Volunteers

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Abstract

Background and purpose: Joint symptoms or join discomfort are defined as the presence of pain, edema, morning stiffness and mobility limitation on most days for a minimum period of six weeks. These symptoms can affect individuals at different ages, leading to functional limitations in daily and professional activities. Treatment of joint symptoms remains symptomatic and is meant to control pain, improve function and quality of life. Abexol is the trade name of a mixture of beeswax alcohols (BWA) with antioxidant, gastro-protective and anti-inflammatory effects (research code: D-002). This double-blind study investigated the effects of Abexol (50-100 mg/day) on patients with joint symptoms for six weeks.

Methods: The primary efficacy outcome was the reduction of the total Western Ontario and McMaster Individual Osteoarthritis Index (WOMAC) score. The secondary efficacy outcome was the reduction on *pain, joint stiffness, physical activity* scores, *and the reduction of the* Visual Analogue Scale (*VAS) score.* Statistical analysis of all data was according to the Intention to treat method.

Results: At study completion Abexol significantly reduced the total WOMAC score ($p<0.00001$ versus baseline and $p<0.0001$ versus placebo) (78.5% versus baseline, 66.5% versus placebo), and the VAS score versus baseline ($p<0.00001$, 63.2%) and placebo ($p<0.0001$, 47.1%). Treatment was safe and well tolerated. Only one patient (placebo group) reported moderate adverse event.

Conclusions: Abexol given for six weeks improved joint symptoms and was safe and well tolerated.

Keywords: *D-002, Abexol, Beeswax alcohols, Joint discomfort, WOMAC score, VAS score*

Introduction

Joint symptoms are defined as the presence of pain, edema, morning stiffness and mobility limitation on most days for a minimum period of six weeks [1]. These symptoms can affect individuals at different ages, leading to functional limitations in daily and professional activities [2].

The health impact of joint symptoms prevalence estimates is difficult to establish because these symptoms are self-reported rather than medically diagnosed. However, there is evidence that both self-reported symptoms and medical diagnosis have good validity [3]. In addition, for population screening, evaluating joint symptoms is more feasible and may be an alternative for prevention, early diagnosis and insertion of interventions. The factors associated with the higher prevalence of joint symptoms are sex, age, overweight and heavy work [4].

Treatment of joint symptoms remains symptomatic and is meant to control pain, improve function and quality of life. The management of joint symptoms included a combination of non-pharmacological interventions and pharmacologic agents [5,6].

The use of analgesics or non-steroidal anti-inflammatory drugs (NSAIDs) to provide symptom relief despite they do not solve the underlying causal pathological process [7,8]. Nevertheless, in view of the gastrointestinal and cardiovascular adverse effects of non-selective NSAIDs and specific ciclooxygenase 2 (COX-2), respectively, the search for better tolerated alternatives is justified [9,10].

Abexol (research code D-002) is a mixture of six high-molecular-weight alcohols (C_{24}, C_{26}, C_{28}, C_{30}, C_{32}, and C_{34}) obtained from beeswax (beeswax alcohols-BWA-), with a product specification of total high fatty alcohols not less than 85% [11]. D-002 has anti-inflammatory effects demonstrated in experimental models of acute and chronic inflammation [12,13]. On the other hand, gastroprotective [14-20] and antioxidant [16,21-26] effects of Abexol have been demonstrated in experimental and clinical studies.

The present study was conducted to investigated the effects of Abexol (50-100 mg/day) administered for six weeks in subjects with joint symptoms.

Materials and Methods

Study Design

The study was prospective, randomized, double-blinded, placebo controlled and conducted in accordance with the Declaration of Helsinki (World Medical Association, revised Brazil 2013) [27], as well as the recommendations of the World Health Organization and the Cuban regulations on Good Clinical Practices. The study protocol was approved by the Ministry of Public Health and by the Ethics Committee in Clinical Research of the Surgical Medical Research Centre, as well as register in the Cuban Public Registry of Clinical Trials.

Subjects were provided oral and written explanations about the nature of the trial and the study treatment in a language easily understood by the subjects in order to request their informed written consent, which was obtained from each of the participants at enrolment.

Eligible subjects were randomised to Abexol (50 mg) or placebo tablets, which should be taken once a day with the breakfast for six weeks, but such dose could be increase to 100 mg (two tablets, one with the breakfast and one with the dinner) whenever the low dose did not provide the expected benefit after week three on treatment. Subjects underwent to visits every 1 week. Physical examinations and assessment of WOMAC and VAS score were done at each visit. Treatment compliance, rescue medication (analgesics) consumption and adverse events were controlled from each visit, laboratory examinations were done at baseline and every three weeks.

Study Participants

Healthy volunteers with joint discomfort symptoms, of both sexes, aged between 20 and 75 years, were enrolled in the trial.

Healthy volunteers with joint discomfort symptoms include subjects with osteoarthritis symptoms that has been classified up to Class II, being:

Class I: Healthy subjects who has no limitation in daily activities.

Class II: Healthy subjects with mild joint discomfort in vocational activities.

Exclusion criteria were to diagnostic arthritis, any arthroscopy within the past year, intra-articular injection of steroids within the past three months, uncontrolled hypertension (diastolic pressure ≥ 120 mm Hg) or diabetes (fasting glucose >7 mmol/L), active liver or renal disease, malignancies, or any other serious illnesses. Also, we excluded pregnant or lactating women, or those not taking adequate contraceptive measures and subjects with the following laboratory abnormalities: alanine -ALT- and/or aspartate amino tranferase-AST >45 U/L, creatinine >130 μmol/L, and/or those with any hospitalization during the six months prior to the study.

Unwillingness to follow-up, to experience adverse event that justified such decision and protocol violations (failure of treatment intake ≥5 days) were predefined causes of premature discontinuations of the study.

Treatment

Study treatments, produced under Licensees and Good Manufacturing Practices conditions, came from the manufacturers (Plants of Natural Products, MEDSOL Laboratory, Havana, Cuba). D-002 content was assessed by using a gas chromatography method. Placebo had similar composition to Abexol tablets, except the active ingredient that was replaced by lactose.

At visit 2, identical coded and packaged tablets of study treatments (Abexol or placebo) were given to study subjects. The randomisation code was computer-generated with a fixed, not stratified randomisation method, using balanced blocks and allocation ratio of 1:1. The dose of Abexol (50-100 mg/day) selected had been shown to produce effective antioxidant effects in clinical studies [16,21-26].

The entire code was kept confidential at the generating place. Sealed individual envelopes with codes of each subject were kept at the generating place and at the site of the Principal Investigator, which should be opened prematurely in case of occurring a serious adverse event, a situation that did not occur in the trial.

Treatment compliance was controlled by counting the remainder tablets and making interviews to subjects. At trial completion, non-used tablets were recovered. Compliance was considered good if the subjects consumed at least 85% of the tablets scheduled from the previous visit.

Subjects were not allowed to consume NSAIDs, steroids, cartilage or calcium supplements, or any other agent that may affect the study outcomes.

Efficacy Assessment

The primary end-point was to obtain a significant reduction of the total Western Ontario and McMaster Individual Osteoarthritis Composite (WOMAC) index [28,29] of not less than 30% as compared to placebo. At each visit, subjects completed the WOMAC questionnaire, which 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).

Reductions in pain, stiffness and physical function scores and reduction of Visual Analogue Scale (VAS) scores [30] were secondary efficacy variables. For efficacy, the score reductions should be significant as compared to placebo.

Safety and Tolerability Assessment

The safety indicators included vital signs (body weight, pulse rate, blood diastolic and systolic pressure), and blood indicators (erythrocyte sedimentation, cholesterol, triglycerides, ALT, AST,

serum fasting glucose and creatinine). Blood biochemical safety indicators were assessed with enzymatic methods by using reagent kits (Roche, Switzerland) and performed in the Hitachi 709 auto-analyser (Tokyo, Japan), erythrocyte sedimentation rate was assessed by conventional method, all done at the clinical laboratory of the Surgical and Medical Research Centre (Havana, Cuba). Controls of the precision and accuracy of the methods were performed.

We considered as adverse event (AE) all undesirable events that occurred to a subject during the study, disregarding the cause, whenever they newly appeared during the trial. Subjects were queried by investigators for any AE between study visits. AE were recorded in the case record forms, including their characteristics, dates of onset and disappearance, treatments adopted and responses achieved. Severity of AE was classified as mild, moderate or serious (SAE), mild being those easily tolerated that not required suspension of study medications and/or specific treatment, moderate those that caused discomfort enough and required stopping therapy and/or specific treatment, and SAE those disabling events that leaded to hospitalisation and/or deaths, if happened. AE that occurred within 30 days of consuming the last study doses, monitored by direct contact with the subjects, were included in this analysis. The causal relationships between AE and the treatments were classified by using the Naranjo algorithm [31].

Statistical Analysis

Data were analysed as per the intention to treat (ITT) approach. So, data of all randomized subjects were included in all analyses. The sample size estimation assumed a difference of ≥30% between the reduction of WOMAC total scores from baseline with D-002 and placebo at study completion. Then, 25 subjects per treatment arm would be sufficient to detect such difference with 80% power and α = 0.05. Assuming a permissible dropout rate of 10%, 55 subjects were enrolled.

Continuous data were analyzed by using the following tests: unpaired and paired t tests, Bonferroni adjustment for multiple comparisons [32], or ANOVA, as appropriate. Categorical variables were compared with the Fisher Exact Probability test. All statistical tests for differences were 2-tailed. The following software was used for the comparisons: Statistics software for Windows (USA) and MS Excel. Statistical significance was taken at the 95% level ($p<0.05$).

Results

Baseline Characteristics

Fifty-five subjects were enrolled in the study. Of them, 50 were eligible for randomization. Five enrolled subjects did not pass to the active treatment step because of the following reasons: fasting glucose >7 mmol/L (3 subjects), creatinine > 130 μmol/L (2 subjects). Of the 50 subjects (29 women, 21 men) (mean age 65 years) included, 50 completed the trial.

All baseline characteristics of both groups were similar, so that subject randomization was effective (Table 1). Gender was predominantly female 29/50 (58%) vs. males 21/50 (42%). Study population included a high frequency (>30%) of some co-morbid conditions like hypertension (64%) and hypercholesterolemia (36%), and some negative lifestyle factors, overweight (48%), like sedentary life (38%) and smoking (22%). A total of 43/50 (86%) randomized subjects consumed some concomitant therapy during the study.

Table 1: Baseline characteristics of study population.

	Abexol (n = 25)		**Placebo (n = 25)**		**Total (n = 50)**	
Age (years) (X ± SD)	65 ± 8		64 ± 9		65 ± 8	
Body mass index (kg/m²) (X ± SD)	26.7 ± 3.2		26.9 ± 3.3		26.8 ± 3.3	
	n	%	n	%	n	%
Class I	1	4.0	1	4.0	2	4.0
Class II	24	96.0	24	96.0	48	96.0
Sex: Women	15	60.0	14	56.0	29	58.0
Men	10	40.0	11	44.0	21	42.0
Personal history						
Arterial hypertension	18	72.0	14	56.0	32	64.0
Overweight (kg/m² ≥ 25, <30)	11	44.0	13	52.0	24	48.0
Sedentary life	11	44.0	8	32.0	19	38.0
Hypercholesterolemia	9	36.0	9	36.0	18	36.0
Smoking	7	28.0	4	16.0	11	22.0
Obesity (kg/m² ≥ 30)	4	16.0	6	24.0	10	20.0
Diabetes mellitus	2	8.0	3	12.0	5	10.0
Trastornos deTiiroides	2	8.0	3	12.0	5	10.0
Coronary disease	1	4.0	1	4.0	2	4.0
Concomitant medications (CM)						
Patients consuming CM	22	88.0	21	84.0	43	86.0
IACE	11	44.0	9	36.0	20	40.0
Diuretics	8	32.0	9	36.0	17	34.0
Lipid lowering drugs	6	24.0	6	24.0	12	24.0
β-blockers	6	24.0	6	24.0	12	24.0
Antiplatelet drugs	2	8.0	4	16.0	6	12.0
Hormones	2	8.0	3	12.0	5	10.0
Oral hypoglycemic drugs	2	8.0	1	4.0	3	6.0
Anxiolytics	2	8.0	1	4.0	3	6.0
Antiulcers drugs	1	4.0	2	8.0	3	6.0
Circulatory	1	4.0	1	4.0	2	4.0

SD: Standard Deviation, n: Number of Cases. *The table includes only those consumed by ≥ 2 subjects.

No significant between group differences were found, (t test for independent samples for continuous variables, Fisher's Exact Probability test for categorical variables).

Efficacy Analysis

Treatment compliance was very good and similar in both groups. At baseline the total WOMAC scores (mean ± SD) in the Abexol and placebo groups were 37.2 ± 7.6 and 37.6 ± 7.2, respectively, without significant differences between the groups (Table 2). At study completion Abexol significantly reduced the total WOMAC score ($p<0.00001$ versus baseline and $p<0.0001$ versus placebo) (78.5% versus baseline, 66.5% versus placebo).

The mean ± SD baseline WOMAC pain scores were 8.5 ± 2.2 (Abexol group) and 8.7 ± 2.4 (placebo) (Table 3). After week 1 of treatment, pain score was significant lower in the Abexol (24.7% reduction versus baseline, p<0.001) and placebo (1.1% reduction versus baseline) groups, so that the net difference versus placebo was 23.6%. The treatment effect was enhanced over the trial, so that at the study completion pain score decreased significantly (p<0.0001) with Abexol (70.6% versus baseline, 56.8% versus placebo).

At baseline the mean stiffness score was 2.8 ± 1.0 in the Abexol group, and 2.9 ± 1.0 in placebo. After week 1, the score was significantly reduced with Abexol (21.4% versus baseline, p<0.001; 18% versus placebo, p<0.01). At study completion the reduction in stiffness with Abexol (p<0.00001 versus baseline, p<0.0001 versus placebo) was of 89.3% as compared to baseline, and of 75.5% versus placebo.

The sequential changes in WOMAC physical function scores were similar to those occurred with the other subset and total WOMAC scores. Meanwhile the mean baseline values of Abexol (26.5 ± 6.0) and placebo (26.3 ± 6.1) groups were similar. The score reductions with Abexol were successively accentuated over the 6 week period, so that the decrease of the physical function score with Abexol at trial completion was of 76.6% and 64.1% as compared to baseline and placebo, respectively.

At baseline the VAS scores (mean ± SD) in the Abexol and placebo groups were 63.1 ± 15.0 and 63.5 ± 16.1, respectively, without significant differences between the groups (Table 4). After week 1 of treatment, the score was significantly reduced in Abexol (p<0.001 versus baseline) and p<0.05 versus placebo. At study completion Abexol had reduced significantly the VAS score (p<0.00001 versus baseline and p<0.0001 versus placebo) (63.2% versus baseline, 47.1% versus placebo)

Table 2: Changes in WOMAC Index scores.

	WOMAC Index scores	
	Abexol	**Placebo**
Baseline	37.2 ± 7.6	37.6 ± 7.2
Week 1	32.1 ± 6.4**	36.7 ± 8.6
% change	-13.7^{+}	-2.4
Week 2	24.2 ± 9.6$^{****+++}$	36.1 ± 9.5
% change	-34.9^{+++}	-4.0
Week 3	21.6 ± 9.4$^{****++++}$	36.2 ± 8.1
% change	-41.9^{++++}	-3.7
Week 4	16.8 ± 8.5$^{****++++}$	35.6 ± 9.6
% change	-54.8^{++++}	-5.3
Week 5	15.2 ± 8.1$^{****++++}$	34.7 ± 9.6**
% change	-59.1^{++++}	-7.7
Week 6	8.0 ± 5.9$^{****++++}$	33.1 ± 8.7**
% change	-78.5^{++++}	-12.0

Values are means ± SD.

**p<0.001; ***p<0.0001 ****p<0.00001 versus baseline (t test for dependent samples) (Bonferroni adjustment).

$^{+}$p<0.05; $^{+++}$p<0.001 $^{++++}$p<0.0001 versus placebo (t test for independent samples).

Safety and Tolerability

Abexol given for six weeks was safe and well tolerated by the patients. The treatment did not affect physical safety indicators, and did not modify significantly the remaining blood indicators laboratory indicators investigated during the study (values not shown for simplicity) in any of the comparisons made. In addition, individual values remained within normal range.

One subject of the placebo group reported moderate adverse event (tendinitis) during the study.

Table 3: Changes in pain, stiffness and physical function scores by treatment group.

	Pain score		Stiffness score		Physical function	
	Abexol	**Placebo**	**Abexol**	**Placebo**	**Abexol**	**Placebo**
Baseline	8.5 ± 2.2	8.8 ± 2.4	2.8 ± 1.0	2.9 ± 1.0	26.5 ± 6.0	26.3 ± 6.1
Week 1	6.4 ± 2.9^{**+}	8.6 ± 2.7	2.2 ± 1.0^{**++}	2.8 ± 0.9	24.2 ± 5.6**	25.6 ± 6.4
% change	-24.7^{+}	-1.1	-21.4^{+}	-3.4	-8.7	-2.7
Week 2	5.4 ± 2.8$^{****+++}$	8.5 ± 2.9	1.6 ± 1.0$^{****+++}$	2.7 ± 1.0	19.2 ± 5.8$^{****+++}$	25.1 ± 6.8
% change	-36.5^{+++}	-2.3	-42.9^{+++}	-6.9	-27.5^{+++}	-4.6
Week 3	5.0 ± 2.7$^{****++++}$	8.3 ± 2.5	1.3 ± 1.0$^{****++++}$	2.6 ± 1.0	14.7 ± 6.5$^{****++++}$	25.0 ± 6.0
% change	-41.2^{++++}	-4.6	-53.6^{++++}	-10.3	-44.5^{++++}	-4.9
Week 4	4.2 ± 2.3$^{****++++}$	8.0 ± 2.6	0.8 ± 0.9$^{****++++}$	2.6 ± 1.0	12.5 ± 7.2$^{****++++}$	24.5 ± 6.5
% change	-50.6^{++++}	-8.0	-71.4^{++++}	-10.3	-52.8^{++++}	-6.8
Week 5	4.0 ± 2.1$^{****++++}$	7.8 ± 2.8	0.6 ± 0.9$^{****++++}$	2.5 ± 0.9	10.1 ± 6.4$^{****++++}$	23.4 ± 6.9*
% change	-52.9^{++++}	-10.3	-78.6^{++++}	-13.8	-61.9^{++++}	-11.0
Week 6	2.5 ± 1.8$^{****++++}$	7.5 ± 2.4	0.3 ± 0.8$^{****++++}$	2.5 ± 0.9	6.2 ± 4.2$^{****++++}$	23.0 ± 6.0*
% change	-70.6^{++++}	-13.8	-89.3^{++++}	-13.8	-76.6^{++++}	-12.5

Values are means ± SD.

*p<0.0083; **p<0.001; ***p<0.0001; ****p<0.00001 versus baseline (t test for dependent samples) (Bonferroni adjustment).

$^{+}$p<0.05; $^{++}$p<0.01; $^{+++}$p<0.001 $^{++++}$p<0.0001 versus placebo (t test for independent samples).

Table 4: Changes in Visual Analogic Scale (VAS).

	VAS Index scores	
	D-002	**Placebo**
Baseline	63.1 ± 15.0	63.5 ± 16.1
Week 1	53.2 ± 17.5**	59.7 ± 18.2*
% change	-16.0+	-7.1
Week 2	49.2 ± 16.5****+	57.9 ± 16.3*
% change	-23.1+	-8.7
Week 3	44.2 ± 17.1****++	57.0 ± 15.8*
% change	-30.8+	-7.6
Week 4	40.0 ± 16.2****++	55.1 ± 15.9**
% change	-34.1+	-15.4
Week 5	35.1 ± 12.8****+++	53.8 ± 17.5**
% change	-40.8+++	-15.4
Week 6	23.2 ± 10.9****++++	53.3 ± 15.1**
% change	-60.2+++	-13.4

Values are means ± standard deviations.

*p<0.0083; **p<0.0001; ****p<0.00001 versus baseline (t test for dependent samples) (Bonferroni adjustment).

+p<0.05; ++p<0.01; +++p<0.001 ++++p<0.0001 versus placebo (t test for independent samples).

Discussion

Using a randomized, double-blind placebo-controlled design the present study demonstrated, that Abexol improved pain in subjects with joint discomfort as compared to baseline and placebo, results consistent with previous clinical study.

Abexol effects were persistent over the trial, so that it produced sustained benefits, distinguishable from placebo.

Abexol and placebo groups were homogeneous at baseline, which indicates that randomization was effective, and that our results are not attributable to initial differences between the groups, but to Abexol treatment. The mean age of study subjects (65 years) falls within that expected for this disease. Most subjects (58%) were women, consistent with a higher prevalence of joint discomfort in women, mainly post-menopausal, a condition present in 29 of the 32 randomized women (90.6%). The high frequency of hypertension (64%), overweight (48%), sedentary life (38%), hypercholesterolemia (36%) and smoking (22%) among study subjects, not only reflects an undesirable occurrence of coronary risk factors, common in Cuban subjects of this age, but agrees with reports of co-morbidity of joint discomfort in middle-aged and older subjects [33].

Both groups displayed an improvement of total WOMAC values over the six weeks of treatment, including placebo, but these reductions, however, were greater in Abexol than in placebo group. A similar picture was seen for subset WOMAC scores. Abexol group significant reductions of the total (primary efficacy variable) and subset (secondary efficacy variables) WOMAC scores were evident from the week 1, with appreciable improvements with continued administration. At study completion pain, stiffness, physical function and total WOMAC scores decreased by 78.5%, 70.6%, 89.3% and 76.6% as compared to baseline, respectively (reductions versus placebo of 66.5%, 56.8%, 75.5%, and 64.1%, respectively). The use of WOMAC questionnaire is used for clinical trials targeting healthy subjects, for evaluating joint protection effects. The treatment with Abexol improves the symptoms and positively impacts on quality of life of affected subjects, consistently with results on VAS score.

At study completion the Abexol group significant reductions of the VAS scores (secondary efficacy variables) by 63.2% versus baseline and 47.1% versus placebo.

In contrast, although reductions with placebo were also seen, they remained almost stationary over the treatment. This improvement with placebo, however, was not totally unexpected, as it can occur in any efficacy measurement based on subjective assessment. Possible explanations for this finding could include that study subjects may have had high expectations of the benefits of study treatments, despite they were due informed about the use of placebo, so that the reductions observed in the placebo group could be influenced by this fact, as in other placebo-controlled studies in subjects with joint discomfort Price et al. 2008) [34].

Only one patient treated with Abexol was titrated to 100 mg/day during the last 3 weeks, a dose adjustment that alone did not seem to explain the differences found between the two groups. The evident significance of the score reductions with Abexol as compared to placebo and the fact that, opposite to the increasingly efficacy of Abexol, the magnitude of the placebo effect was steady over the trial support this appreciation.

There is experimental evidence of the anti-inflammatory effects of D-002, through the inhibition of the activity of the cycle and lipoxygenase enzymes, causes an inhibition of the synthesis of eicosanoids: prostaglandins and thromboxane by the cyclooxygenase route, and leukotrienes and lipoxins by lipoxygenase pathway. D-002 has an effect on COX, specific on COX-2 and on 5-LOX, the latter is involved in the production of leukotrienes B4, which constitutes a potent chemotactic factor for neutrophils, promoting the development of acute inflammation. The inhibition of both enzymes, frame it as a dual anti-inflammatory, blocks the synthesis of eicosanoids, and prevents inflammation associated [35].

The existing concern about the increased risk for cardiovascular disease and stroke with COX-2 inhibitors, and the gastrointestinal and renal complications produced by non-selective NSAIDs [9,10], remains open perspectives for new therapies, including complementary medicines. Some nutraceuticals with anti-inflammatory effects and good gastrointestinal safety profile have shown benefits in patients with joint discomfort Santini et al. 2017) [36,37].

Abexol resulted safe and well tolerated, consistent with previous clinical studies [18-20,22,23,25,26]. In particular, the absence of gastrointestinal adverse events matches well with the gastroprotective effects of Abexol [18-20].

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