Effects of Abexol® (beeswax alcohols) on gastrointestinal symptoms in middle-aged and older subjects

Iván Rodríguez, José Illnait,* Héctor Terry, Rosa Mas,* Lillia Fernández,* Julio César Fernández,* Rafael Gámez,* Meilis Mesa,* Sarahí Mendoza,* Dalmer Ruiz* y Yadira Cruz.***

Centro de Investigaciones Médico Quirúrgicas, *Centro Nacional de Investigaciones Científicas, **Casa de Atención a Combatientes, Plaza de la Revolución, Ciudad de La Habana, Cuba.

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RESUMEN. Los alcoholes de la cera de abejas (ACA) (Abexol®) (anteriormente D-002, mezcla de seis alcoholes alifáticos purificada de la cera de abejas), han demostrado efectos gastroprotectores en estudios experimentales y clínicos. Estudios experimentales demostraron que los ACA reducen el daño gástrico mediante un mecanismo citoprotector multifactorial que involucra, entre otros, efectos antioxidantes sobre la mucosa gástrica y el aumento de la cantidad de mucus gástrico y de su contenido de proteínas totales, glicoproteínas neutrales y macromoleculas sulfatadas, relevantes factores defensivos de la mucosa gástrica. Estudios clínicos previos han demostrado que el Abexol® (ACA) es efectivo en reducir síntomas gastrointestinales comúnmente presente en la población general, en individuos tratados con antiinflamatorios no esteroidales (AINEs) y en pacientes con úlceras duodenales, pero ninguno de ellos había utilizado una escala de síntomas validada internacionalmente. Este estudio aleatorizado, a doble ciegas y controlado con placebo investigó los efectos del Abexol® sobre los síntomas gastrointestinales de sujetos de edad media y avanzada de ambos sexos, sanos por demás, utilizando la Escala Graduada de Síntomas Gastrointestinales (EGSG). Sesenta individuos fueron aleatoriamente distribuidos para recibir tabletas de Abexol® (ACA - 50 mg) o placebo dos veces al día durante 8 semanas. Al culminar la semana 4 de tratamiento, la dosis se aumentó a tres tabletas/d en aquellos sujetos que no percibieron mejoría de los síntomas. Las características basales estuvieron bien balanceadas en ambos grupos. Tras 8 semanas de tratamiento, el Abexol® redujo significativamente ($p < 0{,}000\ 1$) el puntaje total de la escala EGSG respecto a los valores basales y al placebo (40,8 % versus placebo), reducción que resultó significativa desde la segunda semana de tratamiento. La frecuencia de casos que consumieron tres tabletas por día fue menor en el grupo Abexol® (4/30, 13,3 %) ($p < 0{,}01$) que en el placebo (16/30, 53,3 %). Comparado con el placebo, el Abexol® redujo significativamente los síntomas siguientes: acidez/pirosis, regurgitación, distensión abdominal, sensación de vaciado estomacal y flatulencia. El Abexol® no afectó ningún indicador físico o sanguíneo. Hubo siete bajas (cinco placebo, dos Abexol®), pero solo una (placebo) se debió a una experiencia adversa (aumento transitorio de presión arterial). En conclusión, el Abexol® (100 a 150 mg/d) administrado durante 8 semanas mejoró el puntaje total de la escala EGSC (la cual refleja el total de síntomas gastrointestinales) y específicamente, algunos síntomas característicos de trastornos ácido pépticos en sujetos de edad media y avanzada. El Abexol® resultó seguro y bien tolerado. Estos resultados son consistentes con los preliminares de otros estudios clínicos y sustentan la utilidad del Abexol® en sujetos de edad media y avanzada que experimentan síntomas gastrointestinales

ABSTRACT. Beeswax alcohols (BWA) (Abexol®) (formerly D-002, a mixture of six high molecular weight aliphatic alcohols purified from beeswax), has been shown gastroprotective effects in experimental and clinical studies. Experimental studies have proven that BWA reduces the gastric damage through a multifactorial cytroprotective effect that involves antioxidant effects on rat gastric mucosa and the increase of the quantity of soluble gastric mucus and its content of total proteins, neutral glycoproteins and sulphated macromolecules, relevant defensive factors of the gastric mucosa. Previous clinical studies have demonstrated that Abexol® is effective for reducing common gastrointestinal complaints in general population, subjects consuming non-steroidal anti-inflammatory drugs (NSAIDs) and patients with duodenal ulcers, but none of them had used an internationally validated symptom scale. This randomized, double-blinded, placebo-controlled study investigated the effects of Abexol® on the gastrointestinal symptoms of 60 middle-aged subjects of both sexes, otherwise healthy, using the validated Gastrointestinal Symptom Rating Scale (GSRS). Subjects were randomised to receive Abexol® (BWA - 50 mg) or placebo tablets twice a day for 8 weeks. After complete 4 weeks on treatment, the dose was titrated to three tablets/d in those subjects who did not experience symptom improvement. Both groups were well matched at baseline. After 8 weeks on treatment Abexol® reduced significantly ($p < 0.000\ 1$) the total score of the GSRS compared with baseline and placebo (40.8 % versus placebo) after 4 weeks on treatment and that did not wear off at study completion, reduction that was significant from the first 2 weeks on treatment. The frequency of subjects titrated to three tablets a day (lunch, dinner and bedtime) in Abexol®-treated group (4/30, 13.3 %) was lower ($p < 0.01$) than in placebo (16/30, 53.3 %). Compared with placebo, treatment with Abexol® also decreased significantly the following symptoms: acidity/heartburn, regurgitation, bloating, sensation of stomach emptiness & flatulence. Abexol® did not affect any physical or blood safety indicator. There were seven study withdrawals (five placebo, two Abexol®), but only one (placebo) was due to an adverse experience (AE) (transient increase of arterial blood pressure). Concluding, Abexol® (100 - 150 mg/d) given for 8 weeks improved the whole score of the validated GSRS scale, which reflects the overall gastrointestinal symptoms, and specifically improved the several symptoms characteristics of acid-peptic ailments in middle-aged and older subjects. Abexol® was safe and well tolerated. These results are consistent with those of previous clinical studies and support the usefulness of taking Abexol® for middle-aged and older subjects who experience gastrointestinal symptoms.

INTRODUCTION

Yet the burden of disease due to gastrointestinal (GI) diseases is high, as GI diseases are the third most common cause of death.[1] Upper and lower diseases greatly contribute to this fact. GI diseases include gastric and duodenal ulcers, gastritis, gastroduodenal reflux (GERD), non-ulcer dyspepsia and gastric cancer.[1,2] In turn, the most prominent lower GI diseases include colorectal cancer (CRC), inflammatory and non-inflammatory bowel diseases (irritable bowel syndrome).[3,4] Overall, gastric and colorectal cancer, conceived both as life style-related diseases, are within the five most common forms of cancer-related death worldwide.[5,6]

Gastroduodenal damage is not due only to increased acid secretion, but to the imbalance between aggressive and defensive factors.[2] *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs (NSAIDs) are two major aggressive factors for producing gastric mucosal lesions. Stress and anxiety; smoking, alcohol and coffee intake are additional risk factors for ulcers and gastritis.[2]

Although ulcer mortality has been declining recently due to the worldwide decline of *H. pylori* infection,[7,8] NSAID-induced upper GI complications are increasing as expanding elderly population.[9,10] Rates of cardiovascular and cerebrovascular diseases increase with age, therefore, the use of aspirin, the most widely used NSAIDs, increases with age too. In addition, use of other NSAIDs is frequent for many rheumatologic or orthopaedic conditions, like osteoarthritis, a major cause of adult disability. Chronic administration of NSAIDs, however, leads to an increased incidence of upper GI haemorrhages and perforations. Therefore, in a society of large elderly population, NSAIDs-induced GI complications are an important health issue.[11–13]

Additionally, in many subjects upper GI symptoms are critical issues that impair their quality of life and may result in discontinuation of NSAIDs therapy.

Beeswax alcohols (BWA) (Abexol®) (formerly D-002, a mixture of six high molecular weight aliphatic alcohols purified from beeswax), has been shown to prevent the gastric damage induced by non-steroidal anti-inflammatory drugs (NSAIDS), ethanol intake, pylorus ligation and water restrain stress in rats.[14] Also, therapeutic effects of BWA for healing acute (indomethacine-induced) and chronic (acetic acid-induced) gastric ulcers have been proven.[15]

Experimental studies have proven that BWA reduces the gastric damage through a multifactorial cytroprotective effect[16] that involves antioxidant effects on rat gastric mucosa[17] and the increase of the quantity of soluble gastric mucus in normal rats and in rats with ethanol-induced ulcers, increasing the content of total proteins, neutral glycoproteins and sulphated macromolecules of the gastric mucus, relevant defensive factors of the gastric mucosa.[18] In addition, the cytroprotective effects of BWA on ethanol ulcers involves the reduction of increased thromboxane A_2 (TxA_2) and vascular permeability in rat stomach induced by noxious stimuli like ethanol.[16] Likewise, oral treatment with BWA has been shown to prevent cysteamine-induced duodenal ulcers in rats.[19]

The gastroprotective effect of BWA has been linked to its antioxidant effects on rat gastric mucosa, as experimental[17,20-22] and clinical[23-26] studies have reported that it decreases the extent of lipid and protein oxidation, and increases the antioxidant response to the free radical-induced damage. Previous clinical studies have demonstrated that Abexol® is effective for reducing common gastrointestinal complaints in subjects consuming NSAIDs,[27] in middle-aged and older population,[28] and in patients with duodenal ulcers.[29] One of them showed that Abexol® improved symptoms, like acidity/heartburn, asthenia/weakness and bone/joint symptoms and health perception in a general population of middle-aged and older individuals that consumed Abexol® from 15 d to 6 years.[28]

None of these studies, however, have assessed the effects of BWA on the gastrointestinal symptoms by using an internationally validated symptom scale. This randomized, double-blinded, placebo-controlled study, therefore, was undertaken to investigate the effects of Abexol® on the gastrointestinal symptoms of middle-aged and older subjects, otherwise healthy, using the validated Gastrointestinal Symptom Rating Scale (GSRS).[30,31]

Subjects and methods

The study was randomized, double-blinded and placebo-controlled. The ethics committee of the Medical Surgical Research Centre approved study protocol and conduction, which complied with the principles of the Helsinki Declaration and the Cuban guidelines of Good Clinical Practices.

At enrolment, each subject gave informed written consent for participating in the trial, and underwent physical examination and clinical history. Following the initial screening, 60 eligible subjects were randomized to Abexol® (BWA 50 mg) or placebo tablets for 8 weeks. Subjects were advised to continue their usual dietary habits during the trial. An interim check-up and a final visit were done after complete 4 and 8 weeks on treatment, respectively. Subjects underwent physical examination at each visit. Effects on GI symptoms were assessed every 15 d .

Control of treatment compliance and adverse experiences (AE) was controlled at weeks 4 and 8, while laboratory tests were done at baseline and at study completion.

Study participants

The study enrolled men and women (40 – 80 years old) who experienced GI symptoms like abdominal pain, acidity/heartburn, nauseas, flatulence, regurgitation, eructation, abdominal bloating, constipation, diarrhea, occasional vomits, sensation of fast stomach fullness and/or of incomplete emptiness, who were eligible for randomization if they were otherwise in good health according to their medical history, physical examination and laboratory results.

Subjects were excluded from the trial if they had any alarm symptom, like digestive upper or lower bleeding, anemia (haemoglobin < 11 g/L), weight loss (> 10 % of body weight), progressive dysphagia, odinophagia, persistent vomits, personal history of neoplastic diseases, active hepatic, renal or thyroid diseases or both, uncontrolled hypertension (diastolic pressure ≥ 100 mm Hg) or diabetes (fasting glucose ≥ 7 mmol/L), or the following blood values: total cholesterol > 5.2 mmol/L, triglycerides ≥ 2.0 mmol/L, alanine amino transferase (ALAT) > 55 UI, creatinine > 130 μmol/L, or if they had prior history of myocardial infarction, angina, stroke, ischemic transient attacks or major surgery. Also, subjects with family history of gastric cancer or those consuming proton pump inhibitors (PPI), histamine two receptor antagonists (H_2RA), mucoprotective drugs (sucralfate, misoprostol) or any supplement with recognized gastroprotective effects were excluded.

The following reasons were causes of premature study withdrawals: to suffer an AE that justifies such a decision, unwillingness to follow-up and major violations (failure in taking study tablets for ≥ 5 d, intake of supplements or medicines with gastroprotective effects).

Treatments

Abexol® (BWA 50 mg) and placebo tablets, placed in coded identical containers, were given to subjects by progressive inclusion order. Randomization was computer-generated, with a fixed randomization method, using balanced blocks and 1 : 1 allocation ratio. Tablets were taken twice daily with the lunch and dinner for 8 weeks. After complete 4 weeks on treatment, the dose was titrated to 150 mg/d in those subjects who did not experience symptom improvement. The extra tablet (Abexol® or placebo), if required, was consumed at bedtime.

Treatment compliance was assessed by counts of remainder tablets and interviews to subjects. Compliance was good if at least 85 % of the tablets scheduled from the previous visit were consumed.

Consumption of medications or supplements or both with recognized gastroprotective effects was not allowed, except intake of antiacids for symptom relief.

Efficacy variables

The primary efficacy variable was to obtain at least a 20 % significant decrease of the total GSRS score (Spanish edition)[32] compared with placebo. Significant reductions of individual symptoms were considered as secondary efficacy variables. The GSRS scores were also compared in each group between the pretreatment and post-treatment periods.

The GSRS is a self-administered questionnaire for assessing GI symptoms, and consists of 15 items[30-32.] that includes five subscales for reflux, abdominal pain, indigestion, diarrhea, and constipation. The higher the scores, the more pronounced the symptoms. GSRS total scores and the five subscale scores were compared before and every 15 d after beginning treatment.

Safety and tolerability

Safety physical (body weight, pulse rate, blood arterial pressure) and blood (haemoglobin, hematocrit, counts of platelets, red and white blood cells, alanine and aspartate amino transferases —ALAT and ASAT, respectively—, glucose, creatinine, total cholesterol and triglycerides) indicators were assessed.

Adverse experiences were all undesirable events that occurred to a subject during the trial, disregarding its cause, whenever they appeared during the trial. Adverse experiences should be mild, moderate or serious according to their intensity: mild AE did not require stopping the treatments or specific treatment, moderate AE should require therapy discontinuation or specific treatment or both, while serious AE should lead to hospitalization and/or deaths.

According to their causal treatment-relationship, AE were classified as unlikely, doubtfully, possibly, probably or definitively treatment-related. Unlikely treatment-related AE should be absolutely not linked to treatments and caused by identified reasons, doubtfully-related AE should be associated, but not absolutely, with other factors and not expected from previous data. Possibly treatment-related AE should have a time course reasonably consistent with treatment intake and be expected from previous data, but could be also due to other reasons. Probably treatment-related AE should have a time course consistent with treatment intake, should be expected from previous data, but should not be explained by other factors. Finally, a definitely drug-related AE should reach all criteria of a probably drug-related AE, disappear after treatment discontinuation and reappear after restarting the treatment. Since no re-challenge of treatment was done, a definitely drug-related AE should not disappear within one month after treatment completion, which did not occur in this trial.

Laboratory variables

Blood venous samples were obtained after an overnight fast of 10-12 h .

Laboratory safety indicators

Blood biochemistry safety indicators were assessed with enzymatic routine methods using reagent kits (Roche, Switzerland) in the Hitachi 912 autoanalyser (Tokyo, Japan) of the Surgical and Medical Research Centre (Havana City, Cuba), while haematological indicators were determined by routine method using the Sysmex KN 21 equipment located at the same laboratory.

Statistical analysis

Data were analyzed as per intention to treat (ITT). Sample size estimation assumed that differences between mean reductions of GSRS total score from baseline between both groups should be ≥ 20 %. Then, 30 subjects per treatment arm would be sufficient to detect such difference at a 5 % level of significance with 80 % power. Assuming a 10 % of withdrawals, 66 subjects should be enrolled.

Comparisons of continuous data were done with the Wilcoxon test for paired samples, using the Bonferroni adjustment for multiple comparisons in a single test[33] (within-group comparisons) and with the Mann Whitney U test (between-group comparisons). Categorical variables were compared with the Fisher's Exact Test. Tests were two-tailed. A value of $\alpha = 0.05$ was assumed for statistical significance. The statistical software for Windows (U.S.A) was used for statistical comparisons.

RESULTS

Baseline characteristics of study subjects

The study enrolled 66 subjects, of whom 60 were eligible for randomization. Six subjects were not randomized due to be consuming omeprazole (1), thyroid surgery (2), haemoglobin < 11 g/L, glucose > 7 mmol/L (1) ASAT and ALAT values > 55 UI (1). The main demographic characteristic of both groups were well balanced at randomization (Table 1).

Efficacy analysis

Treatment compliance was excellent (> 90 %) and similar in both groups.

Table 2 summarises the effects of Abexol® on the gastrointestinal symptoms assessed through the GSRS. The two study groups had statistically similar values at baseline. Acidity/heartburn, flatulence, regurgitation, sensation of stomach fullness, eructation, abdominal noises and bloating were the most frequent symptoms (> 50 %) of this population.

Alter 2 weeks on treatment, Abexol® significantly ($p < 0.000\ 1$) reduced the whole GSRS score compared with baseline and placebo, when the difference with respect to placebo was 28.2 %. This reduction was enhanced (40.8 %) after 4 weeks on treatment and that did

Table 1. Main baseline characteristics of study population.

	Placebo (n = 30)		Abexol® (n = 30)		Total (n = 60)	
Age (years)[a]	55 ± 10		55 ± 10		55 ± 10	
Body mass index (kg/m²)[a]	25.5 ± 2.9		26.2 ± 4.2		25.9 ± 3.6	
Women (n, %)	18	600	20	66.7	38	63.3
Men (n, %)	12	40.0	10	33.3	22	36.7
Personal history						
Arterial hypertension	10	33.3	12	40.0	22	36.7
Smoking	9	30.0	10	33.3	19	31.7
Diabetes mellitus	1	3.3	0	0.0	1	1.7
Concomitant therapy (CT)	(Consumed by ≥ 3 patients)					
Patients consuming CT	19	63.3	19	63.3	38	63.3
Diuretics	5	16.7	6	20.0	11	18.3
IACE	5	16.7	4	13.3	9	15.0
β-blockers	4	13.3	5	16.7	9	15.0
NSAIDs/analgesics	3	10.0	4	13.3	7	11.7
Asthma relievers	1	3.3	2	6.7	3	5.0
Digestives	1	3.3	2	6.7	3	5.0

[a] (X ± SD) X Media. SD Standard deviation. IACE Inhibitors of angiotensin converting enzyme. NSAIDs: no steroidal anti-inflammatory drugs.

not wear off at study completion. Thus, after 8 weeks on treatment Abexol® reduced significantly the total score of the GSRS compared with baseline and placebo. Compared with placebo, treatment with Abexol® also decreased significantly the following symptoms: acidity /heartburn, regurgitation, bloating, sensation of stomach emptiness & flatulence.

The frequency of subjects titrated to three tablets a day (lunch, dinner and bedtime) in Abexol®-treated group (4/30, 13.3 %) was lower ($p < 0.01$) than in placebo (16/30, 53.3 %).

Safety and tolerability

Abexol® was safe and well tolerated. No significant changes of physical or blood biochemistry indicators were found (Table 3) and individual values remained within normal ranges.

There were seven study withdrawals (five placebo, two Abexol®) (Table 4), but only one (placebo) was due to an adverse experience (AE) (transient increase of arterial blood pressure). Six subjects withdrew from the study due to other reasons: protocol violation (one placebo, two Abexol®), unsatisfactory efficacy (one placebo) and worsened symptoms (two placebo).

Four subjects (three placebo, one Abexol®) referred a total of seven adverse experiences (six in placebo, one in the Abexol® group ($p = 0.051$ 4).

DISCUSSION

This study demonstrates that oral treatment with Abexol® (100 mg/d) for 8 weeks improved gastrointestinal symptoms evaluated through the validated GSRS.

Study subjects were in middle-aged and older subjects (mean age: 55 years old) of both sexes, most of them (38/60, 63.3 %) women, who experienced GI symptoms like abdominal pain, acidity/heartburn, nauseas, flatulence, regurgitation, eructation, abdominal bloating, constipation, diarrhea, occasional vomits, sensation of fast stomach fullness and/or of incomplete emptiness, otherwise healthy.

Since all baseline characteristics were well matched in both groups, they were homogeneous at randomization, which supports that the antioxidant effects here found were treatment-related.

After 15 d on treatment, the effect of Abexol® already reached the efficacy criterion since the net difference of the total GSRS score in the treated group versus placebo was above 20 % (28.2 % versus placebo), and such effect was enhanced (40.8 % versus placebo) at weeks 4 and 8, when the effects were similar. At study completion the total GSRS scope was slightly, but significantly reduced in the placebo group, which could be attributed to a known placebo effect when subjective variables are evaluated.[33-35] Nevertheless, since differences were significant versus placebo and both groups were homogeneous at baseline, such bias did not affect the efficacy assessment, which can be attributed to an actual treatment effect.

The significant reduction of the scores of various items of the GSRS compared with baseline and placebo matches with effects on the most frequent symptoms reported at baseline by study subjects, including acidity/heartburn, among others, are consistent with those of a previous study also conducted in middle-aged and older subjects that found a significant reduction in the rate of reported acidity/heartburn and an improvement of health perception.[28]

Although the occurrence of gastrointestinal complaints does not necessarily involve the presence of

Table 2. Effects of Abexol® on the scores of Gastrointestinal Symptom Rating Scale.

Treatment	Baseline	15	30	45	60
			(d)		
			Abdominal pain		
Placebo	0.5 ± 0.6	0.5 ± 0.7	0.4 ± 0.6	0.3 ± 0.6	0.4 ± 0.7
Abexol®	0.7 ± 0.7	0.3 ± 0.6**	0.3 ± 0.5**	0.4 ± 0.6	0.2 ± 0.5**
			Acidity/heartburn		
Placebo	1.4 ± 0.8	1.0 ± 0.8	1.0 ± 0.7	0.9 ± 0.5	0.8 ± 0.6*
Abexol®	1.5 ± 0.7	0.7 ± 0.8***	0.6 ± 0.8^{***+}	0.6 ± 0.9^{***+}	0.4 ± 0.7^{****+}
			Acid regurgitation		
Placebo	0.8 ± 0.6	0.6 ± 0.7	0.5 ± 0.6	0.5 ± 0.5	0.5 ± 0.5
Abexol®	1.0 ± 0.9	0.6 ± 0.9	0.3 ± 0.6***	0.3 ± 0.7***	0.2 ± 0.6^{***+}
			Sensation of stomach emptiness		
Placebo	1.1 ± 0.8	1.0 ± 0.7	1.0 ± 0.7	1.1 ± 0.8	0.9 ± 0.8
Abexol®	1.1 ± 0.9	0.4 ± 0.7^{***++}	0.2 ± 0.5^{***+++}	0.2 ± 0.4$^{***++++}$	0.3 ± 0.5^{**+}
			Nauseas & vomits		
Placebo	0.4 ± 0.6	0.2 ± 0.4	0.2 ± 0.4	0.2 ± 0.4	0.1 ± 0.3
Abexol®	0.4 ± 0.8	0.2 ± 0.6	0.0 ± 0.0	0.1 ± 0.6	0.1 ± 0.3
			Abdominal noises		
Placebo	0.7 ± 0.7	0.7 ± 0.8	0.7 ± 0.8	0.7 ± 0.7	0.6 ± 0.5
Abexol®	0.8 ± 0.7	0.5 ± 0.6	0.4 ± 0.5**	0.4 ± 0.6**	0.5 ± 0.7
			Abdominal bloating		
Placebo	0.9 ± 0.9	0.7 ± 0.7	0.5 ± 0.6	0.6 ± 0.6	0.7 ± 0.8
Abexol®	0.8 ± 0.8	0.5 ± 0.6	0.2 ± 0.4**	0.2 ± 0.5**	0.2 ± 0.5^{**+}
			Eructation		
Placebo	0.8 ± 0.7	0.8 ± 0.7	0.8 ± 0.7	0.9 ± 0.6	0.9 ± 0.6
Abexol®	0.9 ± 0.9	0.7 ± 0.9	0.6 ± 0.6	0.6 ± 0.7^{+}	0.6 ± 0.7
			Flatulence		
Placebo	1.1 ± 0.7	1.1 ± 0.7	1.0 ± 0.7	1.0 ± 0.7	1.1 ± 0.6
Abexol®	1.1 ± 0.7	0.8 ± 0.7	0.7 ± 0.7	0.8 ± 0.7	0.7 ± 0.8^{**+}
			Slow intestinal transit		
Placebo	0.3 ± 0.6	0.1 ± 0.3	0.1 ± 0.3	0.1 ± 0.3	0.0 ± 0.2
Abexol®	0.1 ± 0.3	0.2 ± 0.4	0.1 ± 0.4	0.1 ± 0.4	0.1 ± 0.4
			Accelerated intestinal transit		
Placebo	0.1 ± 0.2	0.1 ± 0.2	0.0 ± 0.2	0.0 ± 0.0	0.0 ± 0.2
Abexol®	0.1 ± 0.2	0.1 ± 0.2	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
			Soft feces		
Placebo	0.3 ± 0.5	0.3 ± 0.6	0.2 ± 0.4	0.2 ± 0.4	0.1 ± 0.3
Abexol®	0.4 ± 0.6	0.2 ± 0.5	0.1 ± 0.4*	0.1 ± 0.3*	0.1 ± 0.3
			Hard feces		
Placebo	0.5 ± 0.9	0.3 ± 0.6	0.3 ± 0.7	0.2 ± 0.5	0.2 ± 0.6
Abexol®	0.4 ± 0.7	0.2 ± 0.5	0.1 ± 0.4	0.1 ± 0.3	0.1 ± 0.4
			Urgency for defecation		
Placebo	0.3 ± 0.6	0.4 ± 0.7	0.4 ± 0.7	0.4 ± 0.7	0.2 ± 0.6
Abexol®	0.4 ± 0.7	0.3 ± 0.5	0.2 ± 0.6	0.1 ± 0.5	0.2 ± 0.6
			Sensation of incomplete emptiness		
Placebo	0.6 ± 0.8	0.4 ± 0.6	0.4 ± 0.6	0.3 ± 0.6	0.4 ± 0.6
Abexol®	0.5 ± 0.6	0.2 ± 0.5^{*+}	0.1 ± 0.4**	0.1 ± 0.4^{**+}	0.2 ± 0.5^{**+}
			Whole score		
Placebo	9.7 ± 3.4	8.4 ± 3.2	7.7 ± 2.6**	7.5 ± 2.8**	7.0 ± 2.0**
Abexol®	10.1 ± 3.0	5.9 ± 3.5^{****++}	3.9 ± 2.9$^{****++++}$	4.2 ± 3.5$^{****+++}$	4.0 ± 3.2$^{****+++}$

(X ± SD) X Mean. SD Standard deviation. $^{**}p < 0.012\ 5$, $^{***}p < 0.001$, $^{****}p < 0.000\ 1$ Comparisons with baseline. (Wilcoxon test for matched samples) (Bonferroni adjustment), $^{+}p < 0.05$, $^{++}p < 0.01$, $^{+++}p < 0.001$, $^{++++}p < 0.000\ 1$ Comparisons with placebo (Mann Whitney U test).

Table 3. Effects of Abexol® on safety indicators.

Treatment	Baseline	4 weeks	8 weeks
	Effects on physical safety indicators[1]		
	Body weight (kg)		
Placebo	68.10 ± 11.13	67.17 ± 11.36	67.50 ± 12.04
Abexol®	69.37 ± 10.83	69.29 ± 10.99	69.55 ± 10.72
	Pulse rate (beats/min)		
Placebo	70.80 ± 3.66	70.69 ± 3.15	70.64 ± 2.06
Abexol®	71.27 ± 4.18	70.93 ± 5.37	71.54 ± 3.84
	Blood diastolic pressure (mmHg)		
Placebo	79.50 ± 5.78	80.19 ± 5.91	80.40 ± 5.94
Abexol®	77.67 ± 6.40	77.32 ± 7.51	78.75 ± 7.15
	Blood systolic pressure (mmHg)		
Placebo	125.00 ± 10.42	126.35 ± 10.25	124.60 ± 10.98
Abexol®	124.00 ± 13.54	119.82 ± 14.69	121.25 ± 10.15
	Effects on blood safety indicators[1]		
	Hemoglobin (g/dL)		
Placebo	12.57 ± 0.99		12.81 ± 1.36
Abexol®	12.64 ± 1.33		12.81 ± 1.36
	Hematocrit (%)		
Placebo	39.53 ± 3.21		39.94 ± 4.07
Abexol®	40.03 ± 3.61		40.18 ± 3.98
	Red blood cells (cells · 10^6/μL)		
Placebo	4.22 ± 0.39		4.22 ± 0.39
Abexol®	4.32 ± 0.46		4.32 ± 0.46
	White blood cells (cells · 10^3/μL)		
Placebo	5.17 ± 1.08		5.65 ± 1.48
Abexol®	5.74 ± 1.24		5.50 ± 1.74
	Platelets (cells · 10^3/μL)		
Placebo	212.17 ± 54.96		208.76 ± 32.00
Abexol®	218.97 ± 44.78		218.43 ± 41.78
	Aspartate amino transferase (AST) (U/L)		
Placebo	23.13 ± 10.60		24.36 ± 7.13
Abexol®	23.63 ± 9.76		22.79 ± 7.22
	Alanine amino transferase (ALT) (U/L)		
Placebo	23.03 ± 9.52		23.32 ± 10.26
Abexol®	23.17 ± 12.20		23.18 ± 11.40
	Glucose (mmol/L)		
Placebo	4.01 ± 0.68		4.20 ± 0.67
Abexol®	4.08 ± 0.55		4.21 ± 0.46
	Creatinine (μmol/L)		
Placebo	78.63 ± 17.98		76.92 ± 13.57
Abexol®	76.83 ± 12.27		75.82 ± 16.63
	Total cholesterol (mmol/L)		
Placebo	5.04 ± 0.90		5.11 ± 0.90
Abexol®	5.02 ± 1.03		5.17 ± 0.89
	Triglycerides (mmol/L)		
Placebo	1.36 ± 0.76		1.35 ± 0.76
Abexol®	1.42 ± 0.82		1.36 ± 0.67

(X ± SD) X Mean. SD Standard deviation. [1] For simplicity values of physical safety indicators assessed at days 15 and 45 are omitted.

Tabla 4. Adverse experiences (AE) occurred during the study.

	Placebo (n = 30)		Abexol® (n = 30)	
AE	n	%	n	%
Heartburn[1]	1	3.3	0	0.0
Diarrhea[1]	1	3.3	0	0.0
Dyspepsia[1]	1	3.3	0	0.0
Flatulence[1]	1	3.3	0	0.0
Vomits[1]	1	3.3	0	0.0
Throat sore	0	0.0	1	3.3
Transient increase of blood pressure	1	3.3	0	0.0
Total	6	20.0	1	3.3[a]
Total of subjects experiencing AE	3	10.0	1	3.3

n Number of subjects. [1] All these GI-related AE had not been experienced before in these subjects.
[a] p = 0.051 4 Comparison with placebo (Fisher's Exact Probability test).

endoscopic lesions, these symptoms impair the health perception of these individuals and leads to a deteriorated quality of life.

The GSRS, one of the best known specific questionnaires for evaluating the impact of gastrointestinal symptoms, originally developed for use in patients with peptic ulcer and irritable bowel syndrome, has demonstrated good psychometric characteristics when used with a wide variety of gastrointestinal diseases and surgical procedures.[30-32,36] In addition, this scale has been used for evaluating the efficacy of several treatments on gastrointestinal symptoms.[37,38]

The Abexol®-induced improvement of gastrointestinal symptoms assessed by the GSRS is consistent with its gastroprotective effects demonstrated experimentally[14-19] and clinically.[27-29] Among other factors, such effects are mostly mediated by a cytoprotective mechanism that involves several factors, like the increase of the quantity of the soluble gastric mucus (a viscous, adherent gel that is a crucial defensive factor for the gastric mucosa[16,39,40] the improvement of its protein content,[18] and the reduction of the extent of lipid peroxidation in the gastric mucosa,[17] as increased oxidative stress has been linked with gastroduodenal damage.[41-43]

Abexol® did not affect physical and laboratory safety indicators, being safe and well tolerated, in line with prior clinical data,[23–29] and with a complete set of experimental toxicological studies that have not found any BWA-related toxicity.[44-48]

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