Effects of Abexol® in middle-aged and older subjects: an open follow-up

Lilia Fernández Dorta, Héctor Terry,* Ana María Quiñones,* Bienvenida Díaz,* María Luisa Hernández,* José Illnait y Rosa Mas.

Centro de Productos Naturales, Centro Nacional de Investigaciones Científicas, Avenida 25 y 158, Playa, Apartado Postal 6414, Ciudad de La Habana. *Casas de los Combatientes de Ciudad de La Habana (Plaza de la Revolución, Playa, La Lisa, Habana Vieja, Cerro, 10 de Octubre, Arroyo Naranjo), Cuba.

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RESUMEN. Los alcoholes de la cera de abejas (ACA) (Abexol®), codificado anteriormente como D-002, consisten en una mezcla de seis alcoholes de alto peso molecular purificada de dicha cera, con efectos antioxidantes y gastroprotectores demostrados en estudios experimentales y clínicos y efectos anti-inflamatorios demostrados experimentalmente. Los estudios clínicos aleatorizados y controlados constituyen el estándar de oro para demostrar la eficacia y seguridad de un tratamiento, pero la vigilancia farmacológica post-mercadeo los controla en condiciones de práctica clínica rutinaria. El objetivo de este estudio consistió en investigar la tolerabilidad del Abexol® mediante el seguimiento de la incidencia y naturaleza de las experiencias adversas (EA) en sujetos que lo consumían rutinariamente, así como explorar su efecto sobre el alivio de los síntomas y la percepción de salud en estos individuos. En este estudio, se realizó un seguimiento a 1 825 sujetos provenientes de Casas de los Combatientes de Ciudad de La Habana que consumían Abexol® (50 a 150 mg/d), como antioxidante o gastroprotector o ambos. Veintidos casos (1,2 %) abandonaron el tratamiento, ninguno debido a experiencias adversas (EA). La evolución del estado de salud y de los síntomas habituales se siguió en un subgrupo de 184 sujetos. Los síntomas gastrointestinales fueron los más frecuentemente referidos al inicio del estudio (143/184; 77,7 %), seguidos por los relacionados con el cuerpo como un todo (31/184; 16,8 %) y los osteo-articulares (13/184; 7,1 %). Los síntomas individuales más frecuentes (> 5 %) en las condiciones basales fueron: acidez (82/184; 44,6 %), astenia (31/184; 16,8 %) dolor abdominal, (19/184; 10,3 %) y sensación de llenura (12/184; 6,5 %). El tratamiento con Abexol® mejoró la percepción de salud en el 79,9 % de los sujetos con respecto a su condición basal. El Abexol® mejoró la acidez (98,8 %), la astenia (96,8 %) y los síntomas ósteo-articulares (92,3 %) en aquellos sujetos que refirieron el síntoma al inicio del estudio. No se reportaron EA espontáneas lo que confirma la buena tolerabilidad del Abexol® en condiciones de práctica clínica rutinaria. El Abexol® (ACA) mejoró la percepción de salud y los síntomas habituales como acidez, astenia y los síntomas ósteo-articulares. El Abexol® fue bien tolerado en las condiciones de la práctica clínica rutinaria. Estos resultados son consistentes con los obtenidos en estudios clínicos aleatorizados a doble ciegas.

ABSTRACT. Beeswax alcohols (BWA) (Abexol®) formerly coded as D-002, consist in a mixture of six high molecular weight alcohols purified from beeswax, with antioxidant and gastroprotective effects proven in experimental and clinical studies, and anti-inflammatory effects demonstrated experimentally. Randomised, controlled clinical studies are gold standards for demonstrating treatment effects and safety, while post-marketing surveillance should control such data in conditions of routine clinical practice. The objectives of this study were to investigate the tolerability of BWA in adult population by monitoring the incidence and nature of adverse experiences (AE) in subjects taking BWA routinely, and to explore the symptom relief and health perception of these subjects. The present study followed 1 825 subjects treated with BWA (50-150 mg/d) in Veterans Houses of Havana City. BWA was consumed as antioxidant or gastroprotective or both. Twenty-two cases (1.2 %) discontinued the treatment, none due to AE. The evolution of health perception and habitual symptoms was followed in a subgroup of 184 individuals. Gastrointestinal symptoms were those more frequently referred at baseline (143/184; 77.7 %), followed by body as a whole (31/184; 16.8 %) and bone/joint symptoms (13/184; 7.1 %). The most frequent (> 5 %) individual symptoms at baseline were acidity /heartburn (82/184;44.6 %), asthenia/weakness (31/184; 16.8 %), followed by abdominal pain (19/184; 10.3 %) and fullness sensation (12/184; 6.5 %). BWA improved the health perception in 79.9 % of study subjects with respect to baseline conditions. Compared with the condition reported at baseline, BWA improved the following symptoms: acidity/heartburn (98.8 %), asthenia/weakness (96.8 %) and bone/joint symptoms (92.3 %). No AE were spontaneously referred, which confirms the very good tolerability of BWA assessed at conditions of routine clinical practice. In conclusion, Abexol® (BWA) improved health perception and improved habitual symptoms like acidity/heartburn, asthenia/weakness and bone/joint symptoms and was very well tolerated in conditions of routine clinical practice. These results are consistent with those obtained in randomised, double-blind, clinical studies of BWA.

INTRODUCTION

Randomised, controlled studies are the gold standard for demonstrating the effects, safety, and tolerability of a treatment, but post-marketing surveillance studies, at conditions of routine clinical practice, are encouraged for corroborating the safety and tolerability. The usefulness of these studies lies not only in their sample size, larger than in frequent clinical trials, but also in their lack of patient selection criteria, near to the real routine clinical practice.[1,2]

BWA is a mixture of six higher aliphatic primary alcohols purified from the beeswax produced by the bee *Apis mellifera*, L., whose main component (triacontanol) has shown to prevent lipid peroxidation (LP).[3] Likewise, BWA has demonstrated to produce antioxidant effects in experimental and clinical studies, decreasing the extent of LP and increasing the antioxidant response to the damage induced by free radicals[4-9] (and data on file, 2007). Also, BWA has demonstrated to reduce gastric damage or to improve gastric symptoms or both associated to the use of non-steroidal anti-inflammatory drugs (NSAIDS), ethanol intake and other upper gastrointestinal (GI) conditions in experimental and clinical studies.[10-17]

BWA has shown a gastroprotective effect that involves more than a single mechanism, including the antioxidant effects of BWA, proven to be present in rat stomachs,[6] the increase of the quantity, protein and glycoprotein content of the gastric mucus, prostaglandin-dependence and the reduction of the content of thromboxane A_2 (TxA_2) in rat stomachs.[10-12]

Also, oral treatment with BWA produced anti-inflammatory effects in experimental models,[18] which had been also reported for triacontanol,[19,20] the most abundant high molecular weight alcohol in BWA, but such effects have not been demonstrated clinically yet.

Experimental studies of the potential toxicity of BWA have included single and repeat dose studies, genotoxicity tests and studies of foetal and reproductive toxicity that have not found evidences of BWA-related toxicity. Oral doses of BWA of 1 000 and 240 mg/kg administered for 1 year to rats and beagle dogs, respectively, have been Non Observable Adverse Effect Level (NOAEL), supporting the safe consumption of BWA.[21-26]

BWA received marketing authorization in Cuba at 1999. Considering that many middle and older people are currently taking this treatment for terms longer than 12 weeks, the objectives of the study were to investigate the tolerability of BWA in adult population by monitoring the incidence and nature of adverse experiences (AE) in subjects taking BWA in routine practice, and to explore the symptom relief and health perception in subjects attending to the main Veteran Houses of Havana City who have been taking BWA routinely.

SUBJECTS AND METHODS

Study design

This study included subjects that attended to the following Veteran Houses of Havana City: Plaza de la Revolución, Habana Vieja, Playa, La Lisa, Arroyo Naranjo, 10 de Octubre and Cerro, which habitually covered a large population of older individuals. AE were followed and reported at each of these centres.

In addition, symptoms evolution was specifically requested in a subgroup of 184 cases from Playa and La Lisa living areas, for which individual case report forms (CRFs) were filed and reviewed.

Changes in BWA treatment, concomitant medications, duration of treatments and discontinuations were also requested. Adherence to follow-up protocol and uniformity in the procedures followed at each centre were controlled via monitoring visits.

No special risks or conditions were introduced to study patients, since the decision to initiate or discontinue treatment with BWA was based entirely on physicians or subjects' opinions, like occurs in routine clinical practice.

In accordance with Cuban regulations, physicians and patients did not receive any additional payment for participating in this follow-up.

Study population

The present study included reports of all patients who attended the aforementioned sites taking routinely BWA, which was indicated at the physician's discretion based on the product indications and subject characteristics, like to experience recurrent gastric symptoms due to long-term use of aspirin, ethanol intake or some other upper GI conditions (gastroesophageal reflux, gastric or duodenal ulcers or both) or both. BWA was not indicated to subjects known to be hypersensitive to any component of the product.

Patients could discontinue the treatment because of any reason like: lack of perceived benefits, any AE that justified such a decision, cost, or any other reason.

Treatment

Patients consumed BWA 50 mg tablets (Abexol®), being advised to start with BWA at 50 mg/d, but such dose could be increased up to the maximal recommended (200 mg/d) whenever the low dose did not provide the expected benefit after 8-12 weeks on treatment. These recommendations were just guidelines; but physicians or patients or both adapted the dosage depending of subject characteristics and responses.

Compliance

Compliance with BWA was indirectly estimated through patient reports and monitoring of tablets prescribed and purchased. In a subgroup of 184 subjects drug compliance was more strictly followed as per specific request, recorded in the CRFs.

Concomitant therapy

The use of concomitant drugs and changes in BWA regimen occurred during the follow-up was monitored and recorded.

Adverse events or experiences (AE)

Adverse experiences or events (AE) were any undesirable event that occurred to a subject under BWA treatment, disregarding the cause, whenever they newly appeared after commencing the treatment, including those not present at baseline or symptoms that worsened during the treatment.

Information on AE was collected from both spontaneous reports and requests performed and recorded on CRF by study investigators. Data on the onset, duration, specific treatment, and evolution of the AE were recorded. Any AE requiring medical attention during the follow-up period should be carefully recorded, including the hospitalizations and their causes

According to their intensity AE were classified as mild, moderate, or serious. Mild AE were those that should not require medication withdrawal or treatment of the specific AE, moderate AE were those requiring stopping treatment (because of intensity, duration and/or patient perception) and/or specific treatment of the AE, with the exception of asthma attacks requiring albuterol or other short-acting β-agonists in asthmatic patients. Serious AE (SAE) should be disabling or life threatening AE that placed patients at risk, which included those leading to patient hospitalization or death or both.

The possible relationship between the AE and the treatment was classified as unlikely, doubtful, possible, probable, or definite.

Unlikely drug-related AE were those not expected based on the AE profile of BWA and that could be convincingly attributed to external factors, doubtful-related AE did not conform to the AE profile of BWA and should be was most

likely to be caused by other factors. AE should be possibly drug-related if the time course was consistent with BWA administration or the expected AE of BWA or both, although could be attributed to other factors. AE were probably drug-related if the time course was consistent with BWA consumption or the expected pattern of BWA-related AE or both, but could not be explained by other factors. Finally, AE should be classified as definitely drug-related if disappeared after treatment discontinuation and reappeared during treatment rechallenge.

Any AE with some degree of drug-related causality should be considered an adverse drug reaction (ADR).

Data analysis

Because the time of occurrence of some events was uncertain, cumulative incidence of AE should be reported. Descriptive statistics are shown, using continuous or categorical variables.

Mean ± SD values were used for continuous variables, whereas for categorical variables, proportions (numerator /denominator) and percentages were used. Comparisons were done using the difference between two proportions test and the software Statistics for Windows.

RESULTS

Table 1 summarizes the distribution of patients at each Veteran House, which totalised 1 825 subjects (1 489 men, 336 women) treated with BWA. Of them, 1 448 (79.3 %), 360 (19.7 %) and 17 (0.9 %) were treated with BWA 50, 100, and 150 mg/d, respectively. Treatment duration ranged from 15 d to 6 years.

Overall, 22/1 825 subjects (1.2 %) discontinued the treatment, none because of AE, and doctors did not report any AE spontaneously referred in this population.

Table 2 lists the main demographic characteristics of the subgroup of 184 individuals who were interviewed

Table 1. Distribution of cases.

Veteran Houses	Gender		Doses (mg/d)				Total
	Male	Female	50	100	150	200	
Plaza de la Revolución	779	15	794	0	0	0	794
Playa	273	157	430	0	0	0	430
Cerro	206	89	0	295	0	0	295
10 de Octubre	100	40	80	60	0	0	140
La Lisa	67	20	87	0	0	0	87
Arroyo Naranjo	56	6	57	5	0	0	62
Habana Vieja	8	9	0	0	17	0	17
Total	1 489	336	1 448	360	17	0	1 825

Table 2. Characteristics of the subgroup requested about symptoms evolution and health perception.

Characteristic	(n = 184)
Gender n (%)	
Males	102 (55.4 %)
Females	82 (44.6 %)
Age (years) (mean ± SD)	63.4 ± 12.9
Doses (mg/d)	
50	168 (91.3 %)
100	13 (7.1 %)
150	3 (1.6 %)
Treatment taken at	
Early morning (breakfast)	18 (9.8 %)
Noon (lunch)	4 (2.2 %)
Evening meal	103 (56.0 %)
Early morning and evening meal (divided doses)	1 (0.5 %)
Noon and evening meal (divided doses)	8 (4.3 %)
Breakfast, noon and evening meal (divided doses)	2 (1.1 %)
Bedtime	43 (23.4 %)
On demand	5 (2.7 %)
Time on treatment	
Minimum	15 d (1 case)
Maximum	6 years (19 cases)
Average time (mean)	17.8 months

Table 3. Effects of treatment on overall health perception.

Health perception at baseline		Health perception post-treatment		
Quality	n	Improved	Unchanged	Worsened
Good	85	61 (71.8 %)$^{++}$	24 (28.2 %)	0
Fairly good	83	78 (94.0 %)$^{++}$	5 (6.0 %)	0
Poor	10	8 (80.0 %)$^{+}$	2 (20.0 %)	0
No reported	6	–	–	–
Total	184	147/184 (79.9 %)	31/184 (16.8 %)	0

Six individuals had not data about symptoms evolution. $^{+}$ $p < 0.05$; $^{++}$ $p < 0.000$ 1 Comparison with baseline (Differences between two proportions test).

about the evolution of health perception and habitual symptoms. Males outnumbered females (102/184; 55.4 %), but just slightly, so that gender distribution was almost balanced. Most cases (168/184; 91.3 %) consumed the lowest dose (50 mg/d) of BWA, 13/184 (7.1 %) consumed 100 mg/d, while consumption of higher doses was irrelevant (3/184; 1.6 %). Treatment was mainly consumed once daily, with the evening meal (103/184; 56.0 %) or at bedtime (43/184; 23.4 %), followed by consumption at breakfast (18/184; 9.8 %). Divided doses were mainly consumed at noon (with lunch) and evening (dinner) meals (8/184; 4.3 %).

Compared with baseline conditions, study subjects referred improved health perception, disregarding if at baseline they perceived their health as good, fairly good or poor (Table 3).

Thus, 147/184 subgroup subjects (79.9 %) reported to perceive a better health after treatment: 78/83 (94.0 %), 8/10 (80.0 %) and 61/85 (71.8 %) who had referred fairly good health, poor health and good health at baseline referred to perceive improved health.

Table 4 summarises the effects of BWA on the habitual symptoms in this population. Some subjects reported more than one symptom at baseline. GI symptoms (143/184; 77.7 %) were those more frequently referred at baseline, followed by body as a whole (31/184; 16.8 %) and bone/joint symtoms (13/184; 7.1 %). The most frequent (> 5 %) individual symptoms were acidity /heartburn (82/184; 44.6 %), asthenia/weakness (31/184; 16.8 %), followed by abdominal pain (19/184; 10.3 %) and fullness sensation (12/184; 6.5 %).

Compared with the condition reported at baseline, BWA improved specifically the following symptoms: acidity/heartburn (81/82; 98.8 %), asthenia/weakness (30/31; 96.8 %) and bone/joint symptoms (12/13; 92.3 %).

DISCUSSION

The characteristics of the study population are consistent with the indicated claims of BWA therapy and with those of subjects included in randomised, placebo-controlled studies of BWA.

This study demonstrates that BWA enhances health perception in all study subjects and in those who had referred good, fairly good and poor health perception before treatment, assessed in conditions of routine clinical practice. BWA also improved habitual symptoms in study subjects, mainly GI symptoms as a whole, and particularly acidity/heartburn and asthenia/weakness. The composite report of bone/joint symptoms was also improved with BWA.

The present results are consistent in part with the pharmacological effects of BWA. Thus, the improvement of GI symptoms can be associated to the gastroprotective effects of BWA that have been proven experimentally and clinically,[10-17] while the beneficial effects on arthralgia could be related, at least in part, to the anti-inflammatory effects of BWA and triacontanol demonstrated experimentally.[19,20] In turn, the effects of BWA on asthenia/weakness and health perception could be a consequence of these two effects.

More than 50 % of the cases were treated with the lowest dose (50 mg/d), suggesting that physicians adhered to the dosage recommendations. Nevertheless, there were deviations from these recommendations, as might occur in actual clinical practice.

The frequency of withdrawals was low, considering the sample size, age of patients, and duration of follow-up. No discontinuation was due to AE

The good tolerability of BWA is supported by the lack of treatment discontinuations due to AE, and the improved health perception found in the subgroup of 184 cases that was specifically requested about health perception and symptom relief after being treated.

These facts support that the potential risk associated to BWA intake is low, even in a population particularly sensitive to AE and with a high morbidity and mortality rate. The results presented herein are consistent with experimental[21-26] and clinical data[8,9,16,17] (and data on file, 2007) the safety and tolerability of BWA.

CONCLUSIONS

In conclusion, BWA improved health perception and improved habitual symptoms like acidity/heartburn, asthenia/weakness and bone/joint symptoms and was very well tolerated in conditions of routine clinical practice. These results are consistent with those obtained in randomised, double-blind, clinical studies of BWA.

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Table 4. Effects of treatment with BWA on particular symptoms.

Symptoms	n	Subjects referring symptoms changes after treatment		
		Improved	Unchanged	Worst
		Gastrointestinal symptoms		
Acidity/heartburn	82	81 (98.8 %)$^{+++}$	1 (1.2 %)	0
Abdominal pain	19	19 (100.0 %)	0	0
Fullness sensation (floating)	12	12 (100.0 %)	0	0
Dyspepsia	7	7 (100.0 %)	0	0
Slow digestion	6	6 (100.0 %)	0	0
Reflux symptoms	5	5 (100.0 %)	0	0
Swallowing air	4	4 (100.0 %)	0	0
Eructation (blenching)	2	2 (100.0 %)	0	0
Flatulence	2	2 (100.0 %)	0	0
Diarrhoea	2	2 (100.0 %)	0	0
Loss of appetite	1	1 (100.0 %)	0	0
Food intolerance	1	1 (100.0 %)	0	0
Subtotal	143	142 (99.3 %)$^{+++}$	1 (0.7 %)	0
		Bone/joint symptoms		
Arthralgia	6	6 (100.0 %)	0	0
Specific leg pain	7	6 (85.7 %)$^{+}$	1 (14.3 %)	0
Subtotal	13	12 (92.3 %)$^{++}$	1 (7.7 %)	
		Muscular symptoms		
Cramps	1	1 (100.0 %)	0	0
Subtotal	1	1 (100.0 %)	0	0
		Cardiovascular symptoms		
Chest pain	5	2 (40.0 %)	3 (60.0 %)	0
Vein disorders	1	1 (100.0 %)	0	0
Unstable blood pressure	1	1 (100.0 %)	0	0
Subtotal	7	4 (57.1 %)	3 (42.9 %)	0
		Nervous system and special senses		
Headache	2	2 (100.0 %)	0	0
Depressed mood	2	2 (100.0 %)	0	0
Insomnia	1	1 (100.0 %)	0	0
Lack of concentration	1	0	1 (100.0 %)	0
Hearing noise	1	1 (100.0 %)	0	
Subtotal	7	6 (85.7 %)	1 (14.3 %)	0
		Genitourinary		
Diminished libido	2	2 (100.0 %)	0	0
Subtotal	2	2 (100.0 %)	0	0
		Respiratory		
Dyspnea	2	2 (100.0 %)	0	0
Subtotal	2	2 (100.0 %)	0	0
		Body as a whole		
Asthenia/weakness	31	30 (96.8 %)$^{+++}$	1 (3.2 %)	0

Percents calculated with respect to the total symptoms declared at baseline conditions (pre-treatment). $^{+}$ $p < 0.01$, $^{++}$ $p < 0.001$, $^{+++}$ $p < 0.000$ 1 Comparison with baseline (Differences between two proportions test.)

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