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Effect of *Leonurus cardiaca* Oil Extract in Patients with Arterial Hypertension Accompanied by Anxiety and Sleep Disorders

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Leonurus cardiaca **L. (Lamiaceae) is used traditionally for its sedative, hypotensive and cardiotonic effects. Due to the lack of clinical data regarding its effect in patients, a study was carried out to assess the clinical efficacy of Leonurus oil extract (LOE) in patients with arterial hypertension stages 1 and 2, accompanied by anxiety and sleep disorders.**

Fifty patients were treated for 28 days with 1200 mg LOE per day. Positive effects of LOE on psycho-emotional status and arterial blood pressure in patients with stage 1 hypertension were observed 1 week earlier than in patients with stage 2 hypertension. According to the Clinical Global Impression (CGI) scale, a significant improvement in the symptoms of anxiety and depression was observed in 32% of patients, a moderate improvement in 48% and a weak effect in 8%; 12% of patients did not respond to therapy. Side effects were minimal in all groups.

Leonurus oil extract may therefore be a potentially effective therapeutic agent for patients with arterial hypertension and concurrent psycho-neurological disorders. Copyright © 2010 John Wiley & Sons, Ltd.

Keywords: Leonurus cardiaca; oil extract; anxiety; arterial hypertension; sleep disorders.

INTRODUCTION

Psycho-neurological disorders such as generalized anxiety and sleep disorders, which often occur with arterial hypertension, are a major cause of disability. Herbal preparations are frequently used as supportive therapies by patients with psycho-neurological disorders (Astin, 1998; Ernst, 2006). Motherwort, *Leonurus cardiaca* L. (Lamiaceae), is used widely in traditional Russian and other European systems of herbal medicine. It is native to Europe and was popular in ancient Greece, where it was used to calm pregnant women suffering from anxiety. It has been used as a sedative, hypotensive and cardiotonic to treat nervous and functional cardiac disorders since the 15th century (Arber, 1938), and is now the subject of monographs in several pharmacopoeias (European Pharmacopoeia, 2008; State Pharmacopoeia of the USSR, 1990; BHP, 1992). Experimental studies have shown that motherwort can increase coronary blood flow, decrease blood pressure, ameliorate myocardial ischaemia and scavenge free radicals in ischaemic diseases, reducing cellular damage and improving heart function (Zhang *et al*., 1986; Yin and Wang, 2001; Miłkowska-Leyck *et al*., 2002). A refined extract of *L. cardiaca* showed antianginal and antiarrhythmic effects (Ritter *et al*., 2010) and clinical studies have indicated that motherwort can inhibit platelet aggregation, reduce blood coagulation and thrombosis, and improve haemorrheology in patients with coronary heart disease (Zou *et al*., 1989; Liu *et al*., 2007). The plant contains, among its active constituents, labdane diterpenes including leosibirin, leosibiricin and 19-acetoxypregaleopsin; flavonoid glycosides based on querectin and apigenin; the phenylpropanoids eugenol and lavandulifolioside; alkaloids such as stachydrine, betonicine and leonurine, and iridoids including ajugol, ajugoside and harpagide (Kartnig *et al*., 1985; Papanov *et al*., 1998; Miłkowska-Leyck *et al*., 2002; Kosman *et al*., 2002; Liu *et al*., 2007). This pilot study is the first clinical study to investigate the effect of a novel *L. cardiaca* oil extract (LOE) in patients with anxiety, sleep disorders and arterial hypertension.

MATERIALS AND METHODS

Preparation of capsules for administration. *L. cardiaca* herb was extracted with soybean oil (1:10, w/v) using a rotary-pulsation method as described previously (Shikov, 2006; Shikov *et al*., 2008) and encapsulated in soft gelatin capsules. This technology ensures extraction of non-polar and middle polarity compounds (such as iridoids). The medication was produced by the manufacturer Farmagen Ltd (Scheglovo, Russia).

Patients and study design. Fifty male and female patients with arterial hypertension stages 1 and 2, and accompanied by anxiety and sleep disorders, were included into this open, prospective pilot study.

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Inclusion criteria were: age between 18 and 75 years; blood pressure: 140–159/90–99 and 160–179/100–109 mmHg; total cholesterol > 6.5 mmol/L; decreased LDL and increased HDL. Exclusion criteria were: major medical disorders (e.g. myocardial infarct, angina pectoris, hepatic or renal disorders, diabetes), severe concomitant disease, chronic kidney disease (serum creatinine > 2.0 mg/dL), drug dependence, psychotic symptoms, alcohol intake, pregnancy, breast feeding and allergy to plants of the Lamiaceae family.

The LOE was given in soft gelatin capsules containing 300 mg of oil extract (0.15 mg/capsule of iridoids) per capsule in a dose of four capsules (two in the morning, two in the evening) for 28 days.

The treatment response was assessed with the following outcome parameters: dynamics of psycho-neurological symptoms rated on a 5-point SCAG scale: 0, no symptoms; 4, maximum symptoms (Venn, 1983); state – activity – mood (SAM), a subjective patient-rated assessment measuring fatigue (state), reaction time (activity) and emotional condition (mood) on a 7 point numerical rating scale (1, no complaints; 7, maximum complaints) (Doskin *et al*., 1973); and the Clinical Global Impression (CGI) scale (Guy, 1976). SAM scale is based on answers of patients on the questionnaire with 30 pairs of words characterizing fatigue (10 words as such as: vigorous – exhausted; drowsy – excited, etc.), activity (10 words as such as: slow reaction – quick reaction; passive – active, etc.) and emotional conditions (10 words as such as: optimistic – pessimistic; enthusiastic – melancholic, etc). Symptoms were evaluated after 7, 14, 21 and 28 days. At each visit, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate and ECG were documented. Biochemical parameters of blood were analysed at the beginning of the study and after 28 days. At each interview, patients filled in a questionnaire concerning the occurrence of adverse effects during the study. The study was approved by the local ethics committee, registered at the Russian Ministry of Public Health, and was conducted in accordance with the relevant laws of the Russian Federation and ICH GCP guidelines. Prior to entry in the study, written, informed consent was obtained from all patients.

Statistical analysis. Statistical analysis of the data was performed using 'Statistica for Windows' Version 6.0 software. Data were presented as mean value ± standard deviation. The statistical significance of the differences was analysed by Student's *t*-test procedure. Values of $p < 0.05$ were considered to be significant.

RESULTS

Table 1 shows the characteristics of the patients. Six had been diagnosed with chronic bronchitis, nine with arthrosis, six with adenoma of the prostate, ten with osteochondritis and one had gastritis (in remission for 2 years). All patients estimated the tolerability of the LOE extract as excellent.

Subjective complaints of patients with stage 1 hypertension improved after 14 days of treatment, and were significantly different from baseline after 28 days of treatment. Anxiety was reduced in 61%, emotional liability in 53%, headache in 41% and sleep disorders in 47% (Table 2). A statistically significant decrease and normalization in SBP and DBP were noted at 21 days of treatment. Psycho-neurological symptoms were also improved according to the SAM scale after 21 days of treatment, when compared with the baseline by 51% (state), 26% (activity) and 31% (mood). A tendency to a decrease in heart rate (from 81.7 to 75.4) was observed but was not statistically significant.

Table 1. Patient characteristics

Male/female	22/28
Age	
18–33 years	2/4
34–59 years	14/18
60–75 years	6/6
Arterial hypertension	
Stage 1	22
Stage 2	28

In the group of patients with stage 2 hypertension, a reduction in SBP (from 153.3 to 141.6) mmHg and in DBP (from 102.7 to 91.9 mmHg) was achieved after 28 days of treatment (Table 3). Interestingly, a positive improvement in the psycho-emotional status of patients was noted 7 days before the decrease of blood pressure was observed. The reductions in anxiety (62%), emotional liability (20%), headache (34%) and sleep disorders (42%) were seen at day 21, and were sustained for 7 more days of treatment, whereas the maximal decrease of arterial blood pressure was only observed at day 28.

Patients with stage 2 hypertension did not respond to LOE therapy to the same extent. Differences in psycho-neurological symptoms in this group, according to the SAM scale measurements, were not statistically significant compared with baseline. State, activity and mode of patients after 28 days of treatment were improved in 16%, 13% and 15%, respectively, when compared with the baseline (Table 3). The heart rate was stable throughout the study. There were no statistically significant changes in blood biochemical parameters during the study, in either group. These data suggested that LOE was more effective for treatment of patients with stage 1 hypertension.

DISCUSSION

This is the first clinical study to investigate the effects of LOE in patients with psycho-neurological symptoms such as anxiety, sleep disorders, accompanied by arterial hypertension. *L. cardiaca* herb is used traditionally to treat tachyarrhythmia, heart failure and other cardiac disorders (Arber, 1938; Barnes *et al*., 2002). Recently, a refined extract (containing 6.6% of stachydrine) was prepared from *L. cardiaca* using bioassay guided fractionation (Kuchta *et al*., 2009) and its cardiac electrophysiological and antiarrhythmic effects described (Ritter *et al*., 2010). However, in our study antiarrhythmic effects were not observed. The alkaloid leonurine, at a dose 15 mg/kg/body wt/day in mice, has shown significant cardioprotective effects against ischaemia-induced

Table 2. Clinical parameters of patients with stage 1 hypertension at baseline and after 7, 14, 21 and 28 days of treatment with Leonurus oil extract

Parameter	Baseline	7 days	14 days	21 days	28 days
SBP, mmHg	144.5 ± 2.9	141.3 ± 3.7	137.3 ± 4.6	130.3 ± 3.1[a]	129.4 ± 6.2[a]
DBP, mmHg	96.1 ± 1.9	92.1 ± 2.1	90.7 ± 5.1	87.4 ± 3.2[a]	85.9 ± 4.8[a]
Heart rate	81.7 ± 6.9	78.7 ± 5.4	75.9 ± 5.2	76.3 ± 6.3	75.4 ± 5.4
Anxiety, points	1.82 ± 0.51	1.52 ± 0.43	0.71 ± 0.37	0.69 ± 0.51[a]	0.73 ± 0.47[a]
Emotional liability, points	2.36 ± 0.49	1.79 ± 0.46	0.96 ± 0.39[a]	1.16 ± 0.49[a]	1.05 ± 0.50[a]
Headache, points	1.23 ± 0.39	1.13 ± 0.42	0.97 ± 0.41	0.74 ± 0.37[a]	0.79 ± 0.25
Sleeping, points	1.52 ± 0.53	1.31 ± 0.41	0.89 ± 0.35[a]	0.91 ± 0.47[a]	0.96 ± 0.39[a]
State (SAM points)	2.7 ± 0.5	3.2 ± 0.3	3.9 ± 0.5[a]	4.1 ± 0.3[a]	4.0 ± 0.4[a]
Activity (SAM points)	3.1 ± 0.3	3.3 ± 0.4	3.5 ± 0.5	3.9 ± 0.3[a]	3.8 ± 0.5[a]
Mode (SAM points)	3.2 ± 0.5	3.9 ± 0.4	4.1 ± 0.3[a]	4.2 ± 0.3[a]	4.1 ± 0.2[a]

The data are presented as mean ± standard deviation.

[a] Data differ significantly ($p < 0.05$) compared with baseline.

Table 3. Clinical parameters of patients with stage 2 hypertension at baseline and after 7, 14, 21 and 28 days of treatment with Leonurus oil extract

Parameter	Baseline	7 days	14 days	21 days	28 days
SBP, mmHg	153.3 ± 4.6	150.0 ± 3.7	148.2 ± 4.2	145.1 ± 3.4	141.6 ± 4.2[a]
DBP, mmHg	102.7 ± 5.1	103.6 ± 4.6	100.1 ± 4.6	96.5 ± 3.2	91.9 ± 4.3[a]
Heart rate	78.5 ± 7.2	79.1 ± 4.8	78.3 ± 6.1	77.5 ± 6.1	79.6 ± 8.3
Anxiety, points	1.69 ± 0.37	1.27 ± 0.41	0.63 ± 0.36	0.59 ± 0.21[a]	0.64 ± 0.37[a]
Emotional liability, points	2.32 ± 0.39	2.12 ± 0.27	2.09 ± 0.37	1.86 ± 0.39[a]	1.85 ± 0.43[a]
Headache, points	1.42 ± 0.52	1.34 ± 0.32	1.12 ± 0.46	0.93 ± 0.39[a]	0.95 ± 0.27[a]
Sleeping, points	1.92 ± 0.53	1.72 ± 0.33	1.52 ± 0.43	1.12 ± 0.42[a]	1.07 ± 0.41[a]
State (SAM points)	3.7 ± 0.4	3.9 ± 0.3	4.2 ± 0.2	4.5 ± 0.5	4.3 ± 0.4
Activity (SAM points)	3.6 ± 0.4	3.9 ± 0.3	4.1 ± 0.6	4.3 ± 0.4	4.1 ± 0.4
Mode (SAM points)	3.9 ± 0.3	4.2 ± 0.4	4.4 ± 0.5	4.3 ± 0.3	4.5 ± 0.2

The data are presented as mean ± standard deviation.

[a] Data differ significantly ($p < 0.05$) compared with baseline.

myocardial injury (Liu *et al*., 2010), but in the special extract LOE (Shikov, 2006; Shikov *et al*., 2008), alkaloids are absent. Phytochemical profiling of LOE shows the presence of iridoids (500 mg/L) and traces of flavonoids – rutin, quercetin and hyperoside (Pimenov *et al*., 2001; Kosman *et al*., 2002).

Studies have revealed that iridoids exhibit a wide range of bioactivities, including neuroprotective, antitumour, antiinflammatory, antioxidant, cardiovascular, sedative, hypotensive, anxiolytic, choleretic and antispasmodic effects (Tundis *et al*., 2008). Neurological effects documented include: cornel iridoid glycoside (isolated from *Cornus officinalis*), which improved neurological function significantly in a rat model of focal cerebral ischaemia, its mechanism thought to be associated with the expression of vascular endothelial growth factor (VEGF) protein (Yao *et al*., 2009); the iridoid geniposide, which increased social interaction time in mice, demonstrating anxiolytic effects in a dose dependent manner (Toriizuka *et al*., 2005); and harpagide, found in several medicinal plant species, exhibited significant neuroprotective effects against glutamate-induced neurodegeneration in primary cultures of rat cortical neurons (Kim *et al*., 2002). The roots of *Valeriana officinalis* have a long history of use as a sedative medicine in Europe and the iridoid constituents (valepotriates) were shown to reduce the psychic symptoms of anxiety in a randomized placebo-controlled pilot study (Andreatini *et al*., 2002).

The LOE contains 0.15 mg of iridoids (measured as harpagide acetate equivalent) and in this study, showed positive hypotensive, anxiolytic and sedative effects in patients with stage 1 and 2 arterial hypertension accompanied by anxiety and sleep disorders. The effects of LOE on psycho-emotional status and arterial blood pressure in patients with stage 1 hypertension were achieved 1 week earlier than in patients with stage 2 hypertension. This may be due to the fact that functional disorders of the central nervous system are associated with the pathogenesis of stage 1 hypertension, and therefore such patients are more sensitive to sedative and anxiolytic preparations.

A recent clinical study in Singapore and the USA found that patients with later stages of hypertension, or those who survived an acute heart attack, who were taking purified Leonurus extracts showed a significant improvement after 1–3 months of daily consumption of 750–1500 mg of extract (Liu *et al*., 2007). In the present study, a statistically significant ($p < 0.05$) decrease in blood pressure in 11% of patients with stage 1 hypertension and 9% of patients with stage 2 hypertension, was observed on days 21 and 28 of treatment with LOE, respectively (Tables 2 and 3).

According to the CGI scale, 12 patients (24%) reported a great improvement in the symptoms of anxiety and depression with no side effects, whereas four (8%) reported a similar improvement but with mild side effects; 22 patients (44%) reported a moderate

effect with no side effects, with two (4%) reporting a similar moderate improvement with mild side effects; two patients (4%) reported a slight improvement and no side effects, and two (4%) reported a slight improvement and mild side effects. Six patients (12%) did not respond to therapy by LOE. The mild side effects reported by ten patients were a slight delaying of reaction times. This study contributes to the evidence for the therapeutic potential of *L. cardiaca*, specifically the novel oil extract LOE, for the treatment of patients with arterial hypertension accompanied by anxiety and sleep disorders.

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Conflict of Interest

The authors have declared that there is no conflict of interest.

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